VISIT…

Other Natural Products

CHAPTER 28

MASTERING ORGANIC CHEMISTRY

- Recognizing the Structural Features of Terpenes
- Understanding the Hypothetical Mechanisms That Form Terpenes
- Recognizing Steroids and Prostaglandins and the Mechanisms That Form Them
- Recognizing Alkaloids and Fats

THE CARBOHYDRATES, amino acids, proteins, and nucleic acids discussed in Chapters 25, 26, and 27 are sometimes called **primary natural products** because they are found in all types of organisms and are the products of primary metabolism. **Secondary natural products** are usually produced from primary natural product precursors, such as amino acids or acetate ion, and, in general, are less widespread in occurrence. Today, natural product chemistry usually refers to the structure, reactions, and synthesis of these secondary natural products.

Many of these compounds have quite complex structures, often with multiple chirality centers. In addition, many of them are pharmacologically active; that is, they have dramatic physiological effects on any organism that ingests them. For both of these reasons they have always interested organic chemists, and the determination of their structures and their syntheses continue to play an important role in the development of organic chemistry.

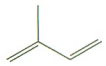
This chapter discusses some of the more important natural products: terpenes, steroids, alkaloids, fats, and prostaglandins. (Fats are primary natural products, but it is convenient to include them in this chapter.) The structures and various aspects of their biosynthesis and chemical reactions are presented in subsequent sections. Because entire books have been written on each of these groups of compounds, the coverage here is necessarily incomplete. However, the intent is to present some of the flavor of their chemistry. Many other classes of naturally occurring organic compounds are not included for reasons of space.

28.1 TERPENES

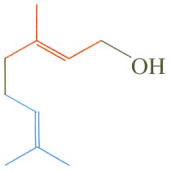
The term **terpene** was originally applied to the compounds obtained from turpentine, an extract from pine trees. Many of the terpenes that were first isolated from

ORGANIC Chemistry Now™
Look for this logo in the chapter and go to OrganicChemistryNow at **http://now.brookscole.com/hornback2** for tutorials, simulations, problems, and molecular models.

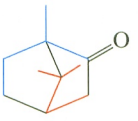
plants had the formula $C_{10}H_{16}$, and it was soon recognized that they could be considered as resulting from the combination of two isoprene units (C_5H_8). Others were found that contain three to six or more isoprene units. (Recall that natural rubber can be viewed as a polymer containing many isoprene units.) Terpenes are now classified as monoterpenes (10 carbons), sesquiterpenes (15 carbons), diterpenes (20 carbons), triterpenes (30 carbons), and so on. Many have various oxygen-containing functional groups. In addition, some do not contain exact multiples of five carbons because carbons have been lost in degradation reactions during their biosynthesis. The structures of several simple terpenes and how they can be considered to be constructed from isoprene units are shown in the following examples. The individual "isoprene units" are shown in different colors.



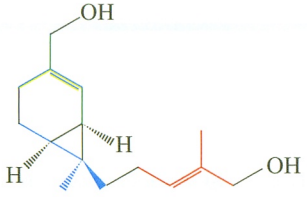
Isoprene



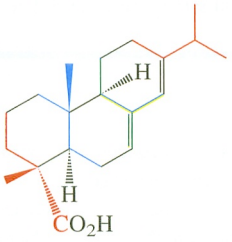
Geraniol
(a monoterpene)



Camphor
(a monoterpene)



Sirenin
(a sesquiterpene)

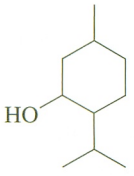


Abietic acid
(a diterpene)

PROBLEM 28.1

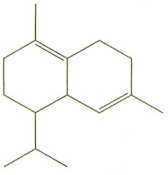
Classify these compounds as monoterpenes, diterpenes, and so on, and show the isoprene units that compose them:

a)



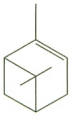
Menthol

b)



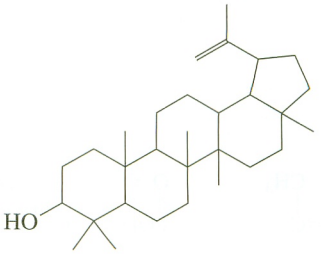
δ-Cadinene

c)



α-Pinene

d)

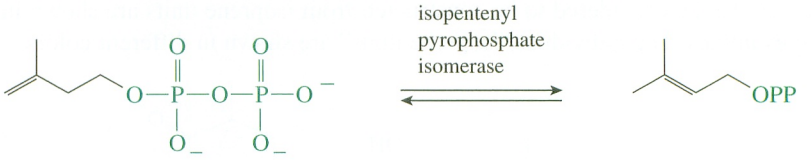


Lupeol

Why do plants synthesize terpenes? In some cases, because of their disagreeable taste, terpenes may act as antifeedants to protect the plant from herbivores. A few are known to be hormones that control plant growth. However, the biological function, if any, of most terpenes is not known. Regardless of their actual purpose, they have served as attractive targets for creative synthetic organic chemists because of their complex structures.

28.2 MONOTERPENES

Monoterpenes, with 10 carbons, can be viewed as resulting from the combination of two isoprene units. Isopentenyl pyrophosphate is the source of these isoprene units in biosynthesis. Dimethylallyl pyrophosphate, which is isomeric with isopentenyl pyrophosphate and is produced from it by the enzyme isopentenyl pyrophosphate isomerase, is also an important intermediate.



Isopentenyl pyrophosphate

Dimethylallyl pyrophosphate

(OPP is used to represent the pyrophosphate group.)

The pathway for the biosynthesis of isopentenyl pyrophosphate is outlined in Figure 28.1. The starting material for this process is represented as acetyl CoA, which

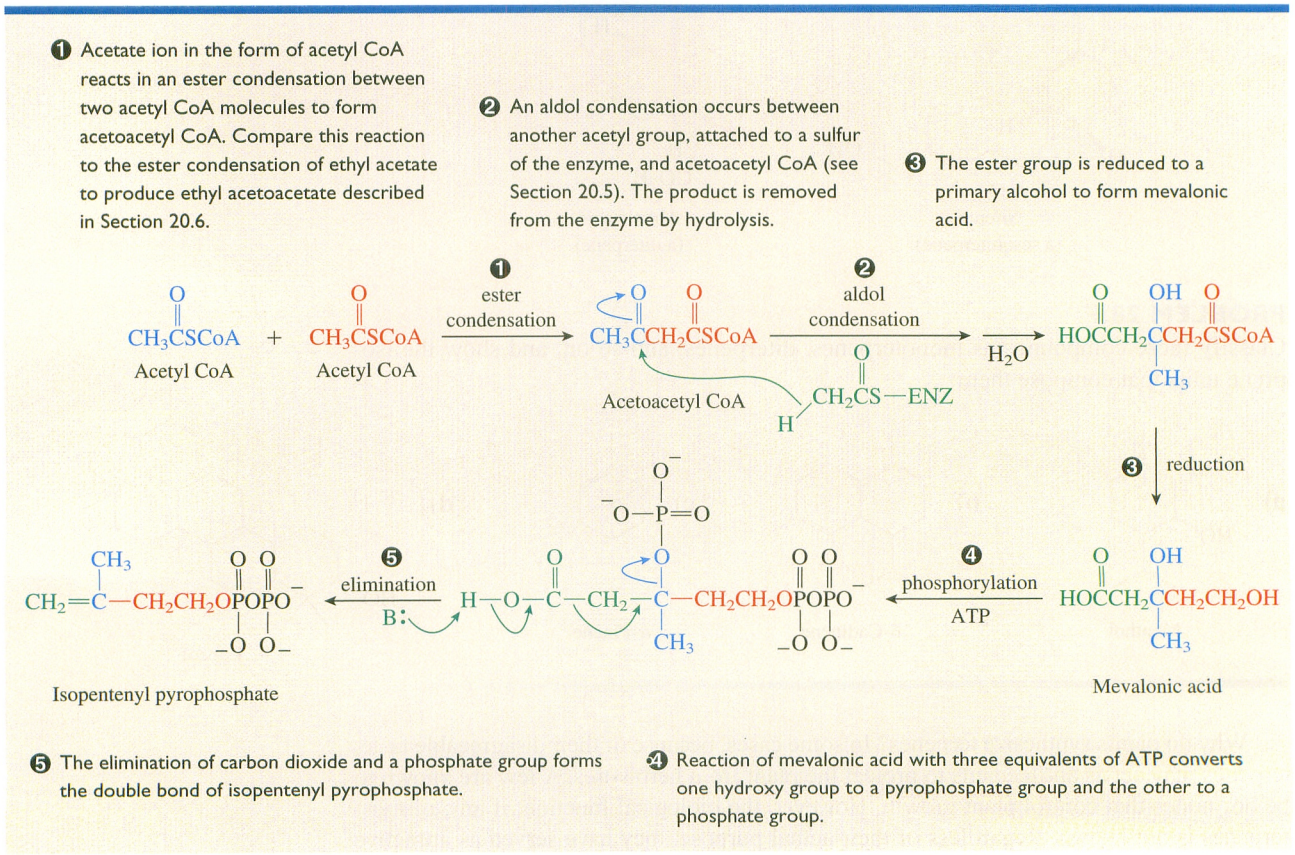

❶ Acetate ion in the form of acetyl CoA reacts in an ester condensation between two acetyl CoA molecules to form acetoacetyl CoA. Compare this reaction to the ester condensation of ethyl acetate to produce ethyl acetoacetate described in Section 20.6.
❷ An aldol condensation occurs between another acetyl group, attached to a sulfur of the enzyme, and acetoacetyl CoA (see Section 20.5). The product is removed from the enzyme by hydrolysis.
❸ The ester group is reduced to a primary alcohol to form mevalonic acid.
Acetyl CoA
Acetyl CoA
ester condensation
aldol condensation
Acetoacetyl CoA
H_2O
reduction
phosphorylation
ATP
elimination
B:
Isopentenyl pyrophosphate
Mevalonic acid
❺ The elimination of carbon dioxide and a phosphate group forms the double bond of isopentenyl pyrophosphate.
❹ Reaction of mevalonic acid with three equivalents of ATP converts one hydroxy group to a pyrophosphate group and the other to a phosphate group.

Figure 28.1

THE CONVERSION OF ACETYL COENZYME A TO ISOPENTENYL PYROPHOSPHATE.

has an acetyl group, from acetate ion, attached to a sulfur of coenzyme A. (The structure of coenzyme A need not concern us here.) The first step in the biosynthesis is a reaction between two acetyl CoA molecules to form acetoacetyl CoA. Although this reaction is controlled by an enzyme, it involves only mechanistic steps that are comparable to those that we have seen in earlier chapters. It is an ester condensation, a reaction that we have seen numerous times (see Section 20.6), and its mechanism is quite similar to the one for an ester condensation that does not involve an enzyme. The next step is an aldol condensation, in which acetoacetyl CoA acts as the electrophile and the nucleophile is derived from another acetyl group attached to a sulfur of an enzyme. Hydrolysis of this compound from the enzyme and reduction produces mevalonic acid. This acid, containing six carbons, is converted to isopentenyl pyrophosphate by phosphorylation followed by elimination of carbon dioxide and a phosphate group.

PROBLEM 28.2

Show the mechanism for the ester condensation shown in the first step of the process outlined in Figure 28.1. Assume that the reaction is caused by base and ignore the effect of the enzyme.

PROBLEM 28.3

Show the mechanism for the aldol condensation shown in the second step of the process outlined in Figure 28.1. Assume that the reaction is caused by base and ignore the effect of the enzyme.

The pyrophosphate group (OPP) is a good leaving group. Much of the chemistry involved in the biosynthesis of terpenes can be understood on the basis of the reactions of carbocations that are formed when the pyrophosphate group departs from compounds such as isopentenyl pyrophosphate or dimethylallyl pyrophosphate. Thus, the formation of geranyl pyrophosphate, the parent compound for the monoterpenes, can be viewed as resulting from the addition of the carbocation produced from dimethylallyl pyrophosphate to isopentenyl pyrophosphate as shown in Figure 28.2. However, it is important to remember that these reactions are controlled by enzymes. As such, they do not involve free carbocation intermediates, and they are often more concerted than the "mechanisms" shown in this chapter. Nevertheless, these "mechanisms" serve to show that these enzyme reactions are not magic but follow the same rules presented in previous chapters for carbocation behavior. The enzymes serve to lower the activation barriers for the overall processes and to control the stereochemistry, regiochemistry, and selectivity of each reaction.

PROBLEM 28.4

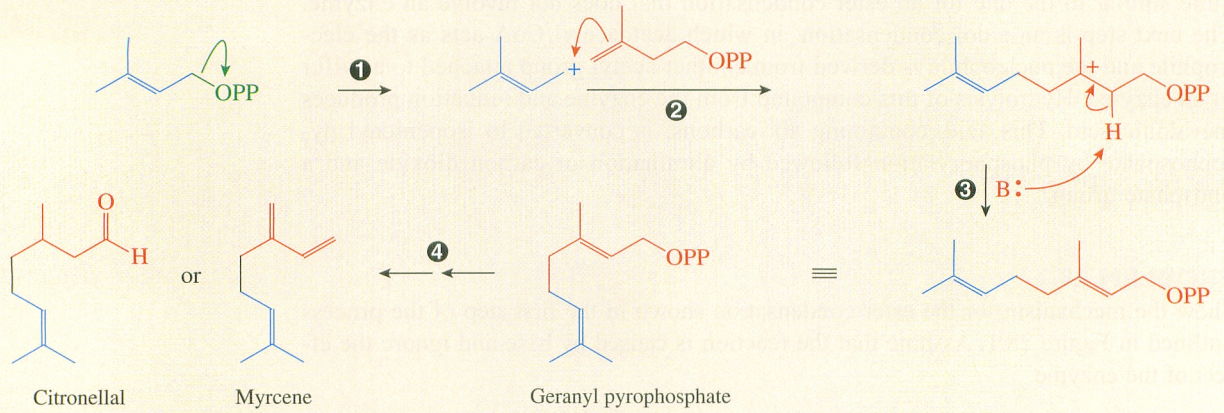
Show the structure of the species derived from the pyrophosphate leaving group after it has departed and explain why it is a good leaving group.

As shown in Figure 28.2, the allylic carbocation that is produced after pyrophosphate has left from dimethylallyl pyrophosphate adds to the double bond of isopentenyl pyrophosphate to produce a new carbocation containing 10 carbons. Loss of a proton from this carbocation produces geranyl pyrophosphate, which serves as the precursor

❶ Pyrophosphate is a weak base and thus a good leaving group. It leaves from dimethylallyl pyrophosphate to produce an allylic carbocation.

❷ The carbocation then adds to the double bond of isopentenyl pyrophosphate to produce a new carbocation that contains 10 carbons. Note that this addition follows Markovniknov's rule.

❸ Loss of a proton from this carbocation produces geranyl pyrophosphate, which, with its 10 carbons, is the parent compound for the monoterpenes.



❹ Simple transformations (hydrolysis of the pyrophosphate group to a hydroxy group, elimination, oxidation, etc.) convert geranyl pyrophosphate to monoterpenes such as geraniol, myrcene, and citronellal.

Figure 28.2

THE CONVERSION OF ISOPENTENYL PYROPHOSPHATE AND DIMETHYLALLYL PYROPHOSPHATE TO GERANYL PYROPHOSPHATE.

for the formation of the monoterpenes. For example, elimination of the pyrophosphate group from geranyl pyrophosphate produces myrcene, and hydrolysis of the OPP group to an alcohol produces geraniol, a terpene obtained from roses and used in many perfumes because of its roselike odor. Reduction of the double bond of geraniol and oxidation of the hydroxy group to an aldehyde produces citronellal, a terpene found in lemon-grass oil that is also used as an ingredient in perfumes and in candles that are used to repel mosquitoes.

PROBLEM 28.5

The conversion of geranyl pyrophosphate to myrcene follows an E1 mechanism. Show the steps in this mechanism.

Isomerization of the double bond of geranyl pyrophosphate from *E* to *Z* produces neryl pyrophosphate. As shown in Figure 28.3, the carbocation that is formed from neryl pyrophosphate can cyclize to a new carbocation that contains a six-membered ring. Nucleophilic addition of water to this carbocation produces α-terpenol, whereas loss of a proton produces limonene, a monoterpene with a lemonlike odor that occurs in citrus fruits. Further transformations lead to other monoterpenes, such as menthol,

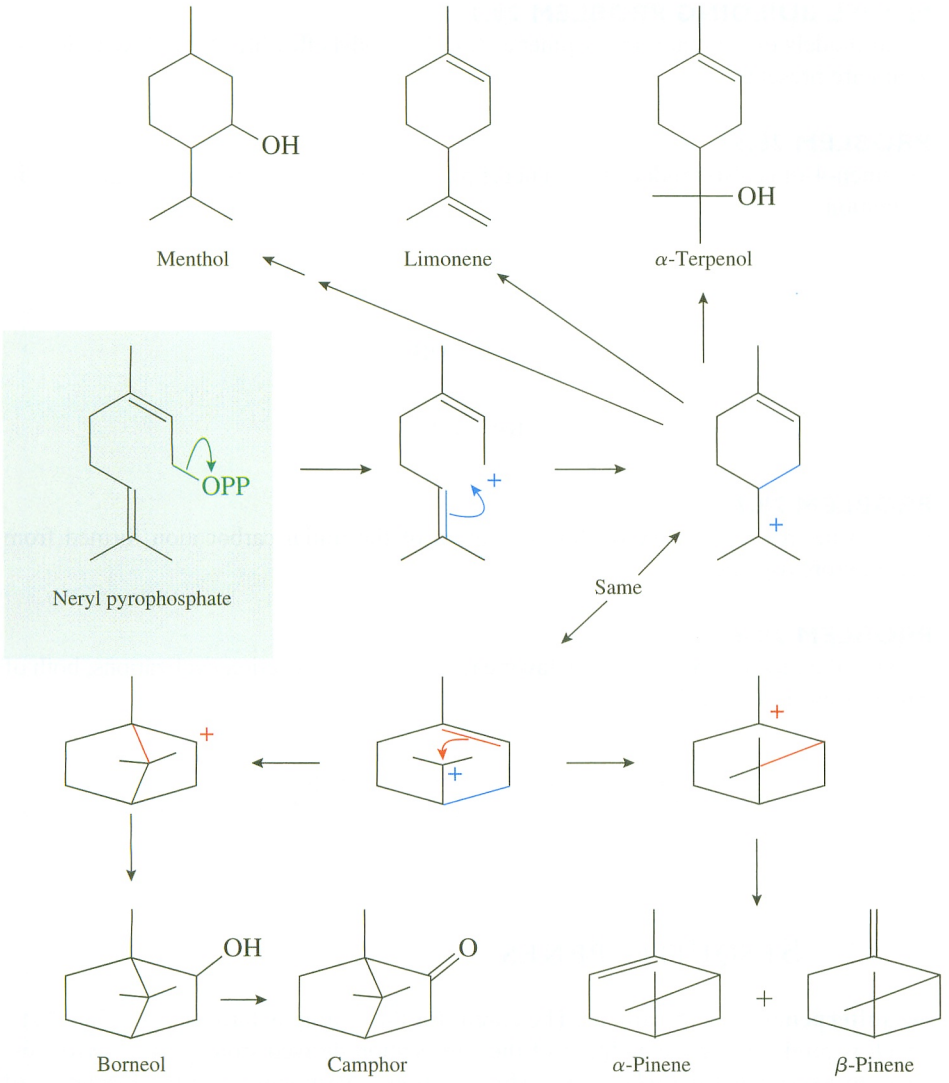


Figure 28.3

THE FORMATION OF SOME CYCLIC AND BICYCLIC MONOTERPENES FROM NERYL PYROPHOSPHATE.

which is a major component of oil of peppermint and is used as a flavoring for foods, toothpastes, and mouthwashes.

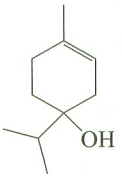
The cyclic carbocation produced from neryl pyrophosphate can also cyclize a second time by adding to either end of the double bond of the six-membered ring (see Figure 28.3). The two resulting carbocations are said to be bicyclic (having two rings) and give rise to various bicyclic monoterpenes such as borneol and camphor (which smells like mothballs and is used in cosmetics, liniment, and anti-itching medications) and α- and β-pinene, two of the major components of turpentine.

MODEL BUILDING PROBLEM 28.1

Build models of camphor and α-pinene. Are the models flexible at all? What kinds of strain are present?

PROBLEM 28.6

Terpinen-4-ol is also produced from neryl pyrophosphate. Suggest a mechanism for its formation.



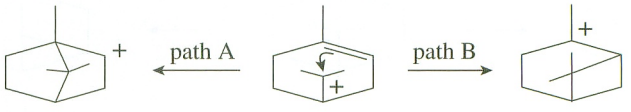
Terpinen-4-ol

PROBLEM 28.7

Explain the regiochemistry of the cyclization of the initial carbocation formed from neryl pyrophosphate.

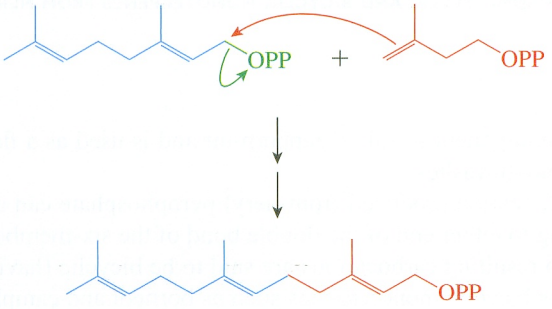
PROBLEM 28.8

Explain the factors that favor or disfavor each of these carbocation cyclizations, both of which occur in Figure 28.3:



28.3 SESQUITERPENES

Sesquiterpenes have 15 carbons. The parent for this family is farnesyl pyrophosphate, which is produced by the addition of the carbocation derived from geranyl pyrophosphate to isopentenyl pyrophosphate. This reaction is very similar to the formation of geranyl pyrophosphate shown in Figure 28.2.



Farnesyl pyrophosphate

In a process that is quite similar to the formation of the cyclic monoterpenes, isomerization about the double bond of farnesyl pyrophosphate, followed by carbocation

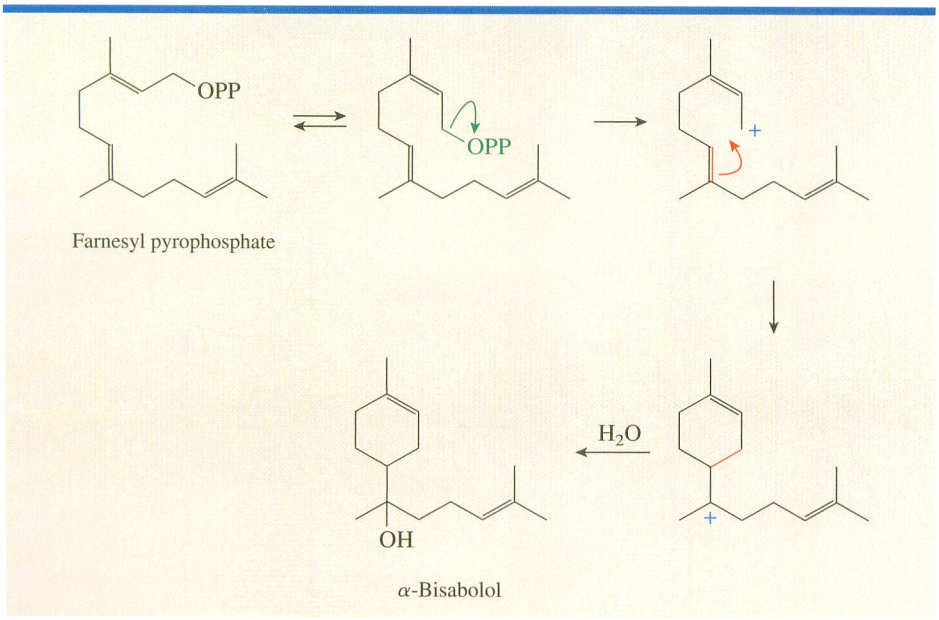


Figure 28.4

FORMATION OF A CYCLIC SESQUITERPENE FROM FARNESYL PYROPHOSPHATE.

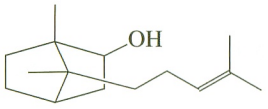
formation and cyclization, results in the production of cyclic sesquiterpenes such as α-bisabolol (see Figure 28.4).

PROBLEM 28.9

Explain the regiochemistry of the carbocation cyclization shown in Figure 28.4.

PROBLEM 28.10

Suggest a mechanism for the formation of campherenol from farnesyl pyrophosphate:



Campherenol

Farnesyl pyrophosphate can also cyclize in a quite different manner that does not involve the pyrophosphate group, as illustrated in Figure 28.5. This process is initiated by protonation of the double bond at the opposite end of the chain from the pyrophosphate group. The resulting carbocation adds to the double bond in the center of the chain, forming a six-membered ring. This is the ring system present in sesquiterpenes such as abscisic acid, a plant hormone that controls the shedding of leaves. The carbocation can also add to the remaining double bond to produce a bicyclic system of two six-membered rings that share one ring bond. This is illustrated in Figure 28.5 by the formation of drimenol. The cyclic structure present in drimenol, with its two fused six-membered rings, is especially important in natural

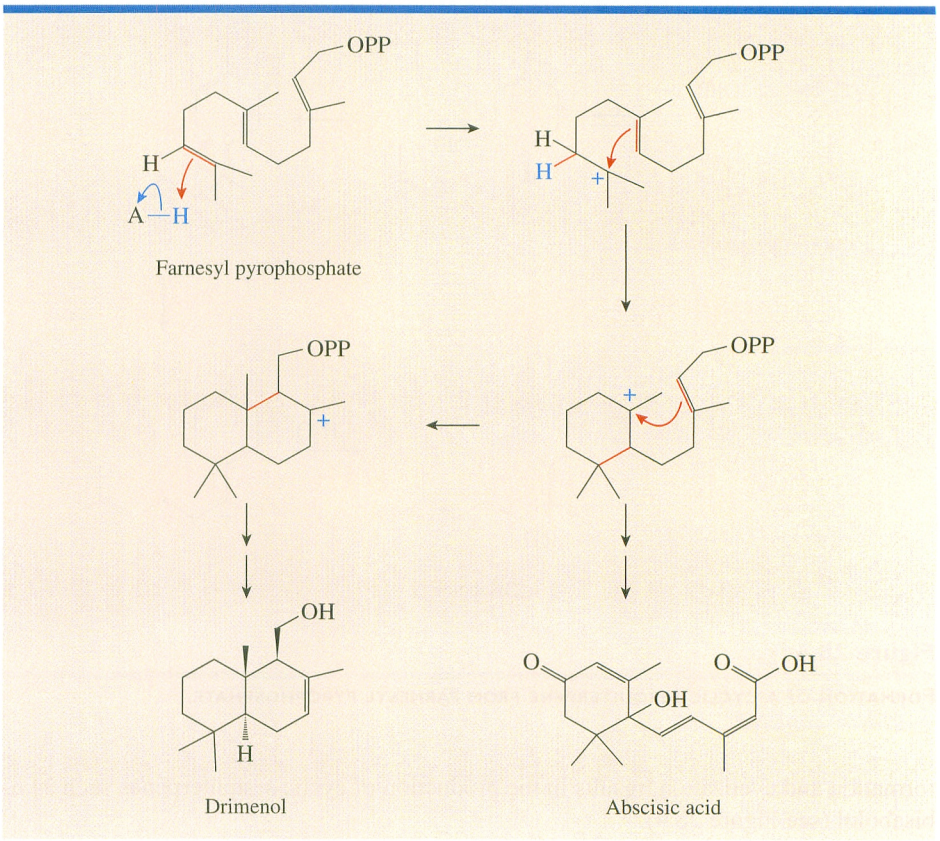


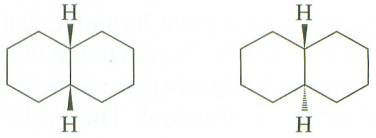
Figure 28.5

AN ALTERNATIVE CYCLIZATION OF FARNESYL PYROPHOSPHATE.

products chemistry. The parent bicyclic ring would be produced by the addition of 10 hydrogens to naphthalene, so it is known as decahydronaphthalene, which is often shortened to decalin.

Naphthalene — Decahydronaphthalene or decalin

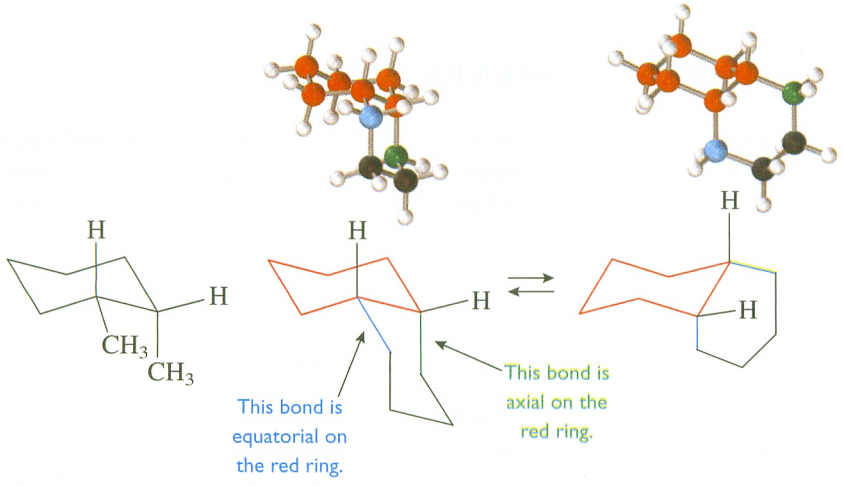
Decalin has two saturated six-membered rings fused together; that is, the rings share a common bond. The hydrogens at the ring junctions may be attached on the same side or on opposite sides, so there are two stereoisomers: *cis*-decalin and *trans*-decalin. Neither of these is chiral.



cis-Decalin — *trans*-Decalin

The fused six-membered rings of decalin are still cyclohexane rings, and like most cyclohexane rings, they prefer chair conformations. Analysis of the conformational preferences of these molecules is very similar to that of 1,2-dimethylcyclohexane (see Chapter 6). Recall that *cis*-1,2-dimethylcyclohexane has one methyl group axial and one equatorial and that a ring-flip produces a new chair conformation in which the axial methyl group has become equatorial and vice versa. Likewise, *trans*-1,2-dimethylcyclohexane has two conformers, one with both methyl groups equatorial and one with both groups axial.

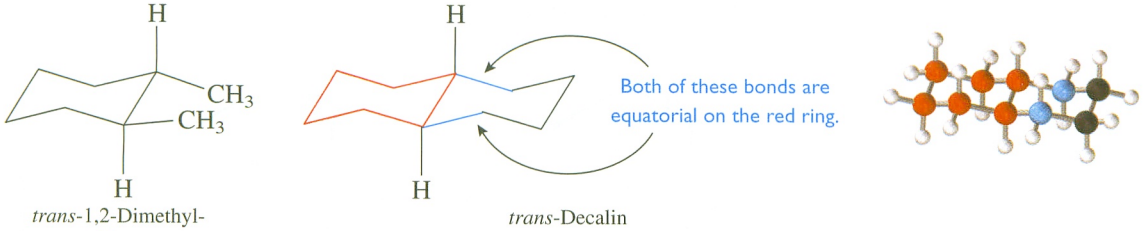
In the case of the decalins, both rings assume chair conformations. For *cis*-decalin the carbons of the first ring are attached to an axial position and an equatorial position of the second ring, just like the methyl groups of *cis*-1,2-dimethylcyclohexane. Likewise, the carbons of the second ring are attached to an axial and an equatorial position of the first ring. A ring-flip, which interconverts axial and equatorial positions, can occur.



cis-1,2-Dimethylcyclohexane

cis-Decalin

For *trans*-decalin, both carbons of one ring are attached to equatorial positions of the other. This is true for both rings. The molecule is rigid and cannot undergo a ring-flip because one ring is not large enough to bridge axial positions, which point in opposite directions, on the other. As was the case with the 1,2-dimethylcyclohexanes, *trans*-decalin, with both rings attached equatorially to the other, is more stable than *cis*-decalin by 2.7 kcal/mol (11.3 kJ/mol). Decalin rings, especially those with *trans*-stereochemistry, are an important part of many natural products, including terpenes and steroids (see Section 28.5).



trans-1,2-Dimethylcyclohexane

trans-Decalin

MODEL BUILDING PROBLEM 28.2

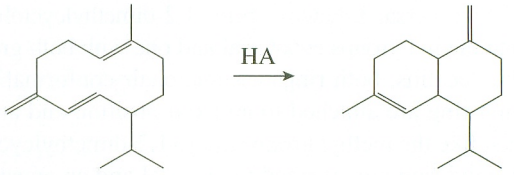
Build models of *cis*- and *trans*-decalin and examine the conformational mobility of each.

PROBLEM 28.11

Discuss the regiochemistry of each carbocation reaction shown in Figure 28.5.

PROBLEM 28.12

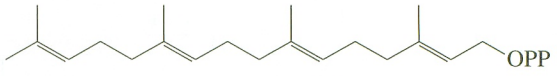
Suggest a mechanism for the conversion of germacrene D to γ-cadinene:



Germacrene D γ-Cadinene

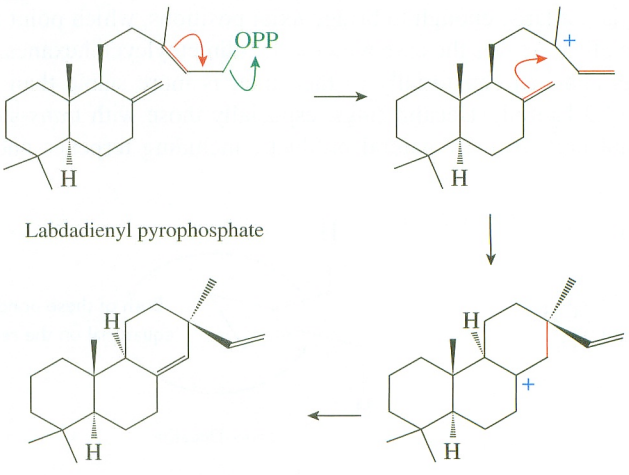
28.4 LARGER TERPENES

The larger terpenes are formed in the same manner as the monoterpenes and sesquiterpenes. The precursor for the diterpenes is the C_{20} compound geranylgeranyl pyrophosphate, which is formed from farnesyl pyrophosphate in a manner similar to that shown in Figure 28.2:



Geranylgeranyl pyrophosphate

Geranylgeranyl pyrophosphate can cyclize in many different ways to produce a wide variety of diterpene ring systems. As one example, cyclization initiated by protonation of the double bond most remote from the pyrophosphate group produces the decalin ring system of labdadienyl pyrophosphate in a reaction that is nearly identical to the cyclization shown in Figure 28.5. Further cyclization, initiated by departure of the pyrophosphate group and proceeding along the lines of those shown in Figures 28.3 and 28.4, produces the tricyclic diterpene pimaradiene:



Labdadienyl pyrophosphate

Pimaradiene

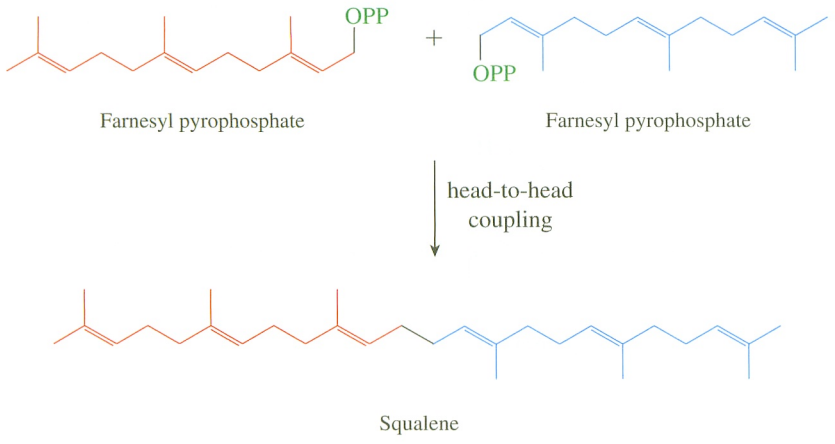
PROBLEM 28.13

Suggest a mechanism for the conversion of geranylgeranyl pyrophosphate to labdadienyl pyrophosphate.

PROBLEM 28.14

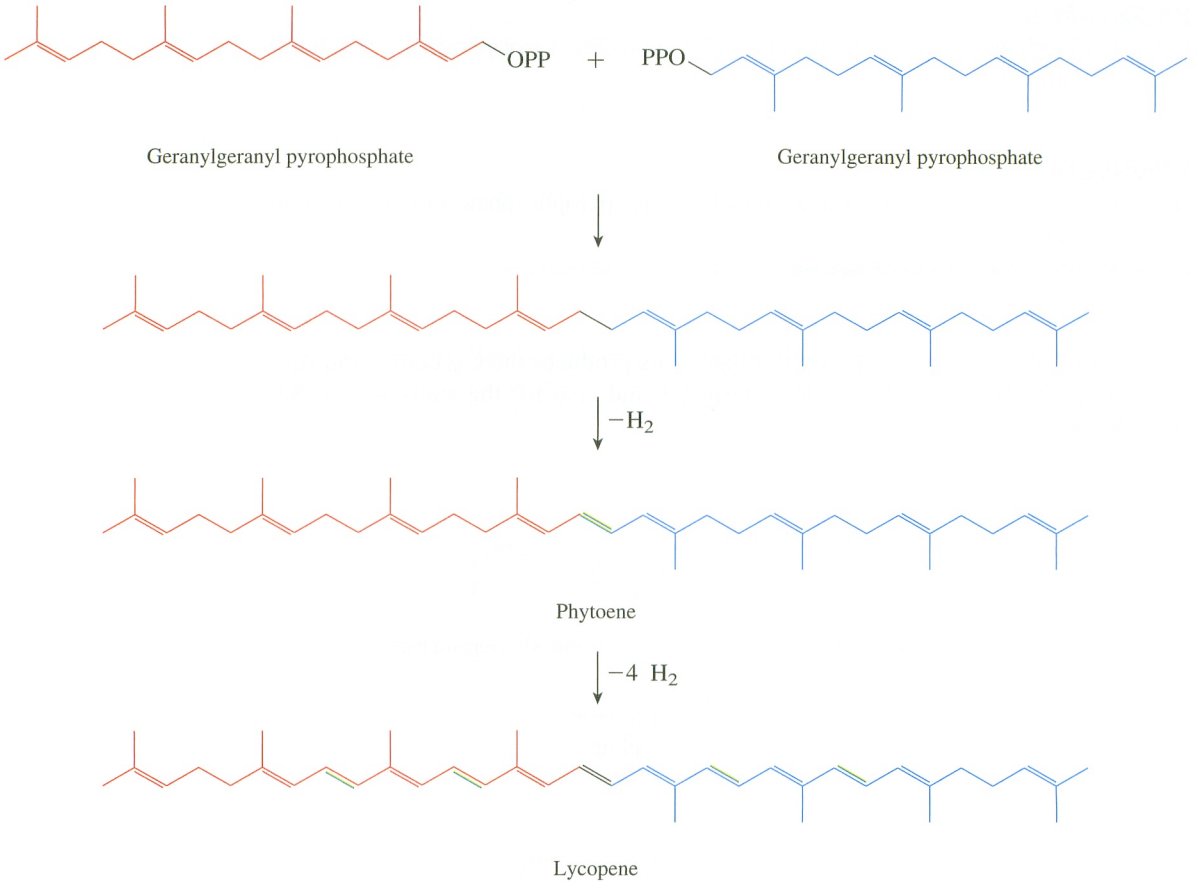
Suggest a mechanism for the conversion of geranyl pyrophosphate to geranylgeranyl pyrophosphate.

Coupling of two C_{15} farnesyl pyrophosphate units produces the C_{30} compound squalene, which is the precursor for the triterpenes and also for the steroids (see Section 28.6):



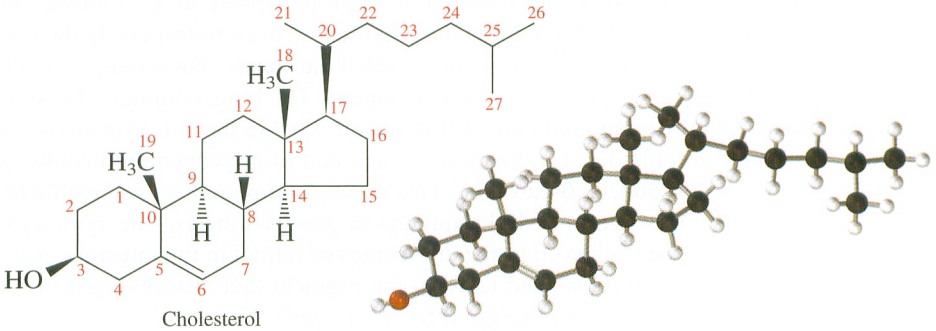
Note that the formation of squalene results from the coupling of both of the farnesyl groups at the carbons attached to the pyrophosphate groups (head-to-head coupling) and that both pyrophosphate groups are lost during this process. The mechanism for this reaction differs dramatically from that shown in Figure 28.2 and is too complicated to present here.

A similar coupling of two C_{20} geranylgeranyl pyrophosphate units, followed by dehydrogenation, produces the C_{40} compound, phytoene. This tetraterpene is the precursor for an important group of compounds called carotenes. For example, additional dehydrogenation of phytoene produces lycopene. The long, conjugated system of double bonds of this compound causes it to absorb visible light. Lycopene is the red pigment found in tomatoes. Cyclization of each end of a lycopene molecule, as shown in Figure 28.6, produces β-carotene. This orange compound is responsible for the color of carrots and serves as a light antenna in photosynthesis. The symmetrical compound β-carotene is cleaved to two molecules of retinal in the intestine. Retinal, also known as vitamin A, is used to form the pigment that absorbs light in the retina of the eye. So carrots really are good for your eyes!



28.5 STEROIDS

Perhaps the best-known steroid—or at least the most notorious—is **cholesterol.** Like all steroids, it has a tetracyclic ring system consisting of three fused six-membered rings and one five-membered ring. The structure of cholesterol and the standard numbering for the steroid ring system are shown in the following diagram:



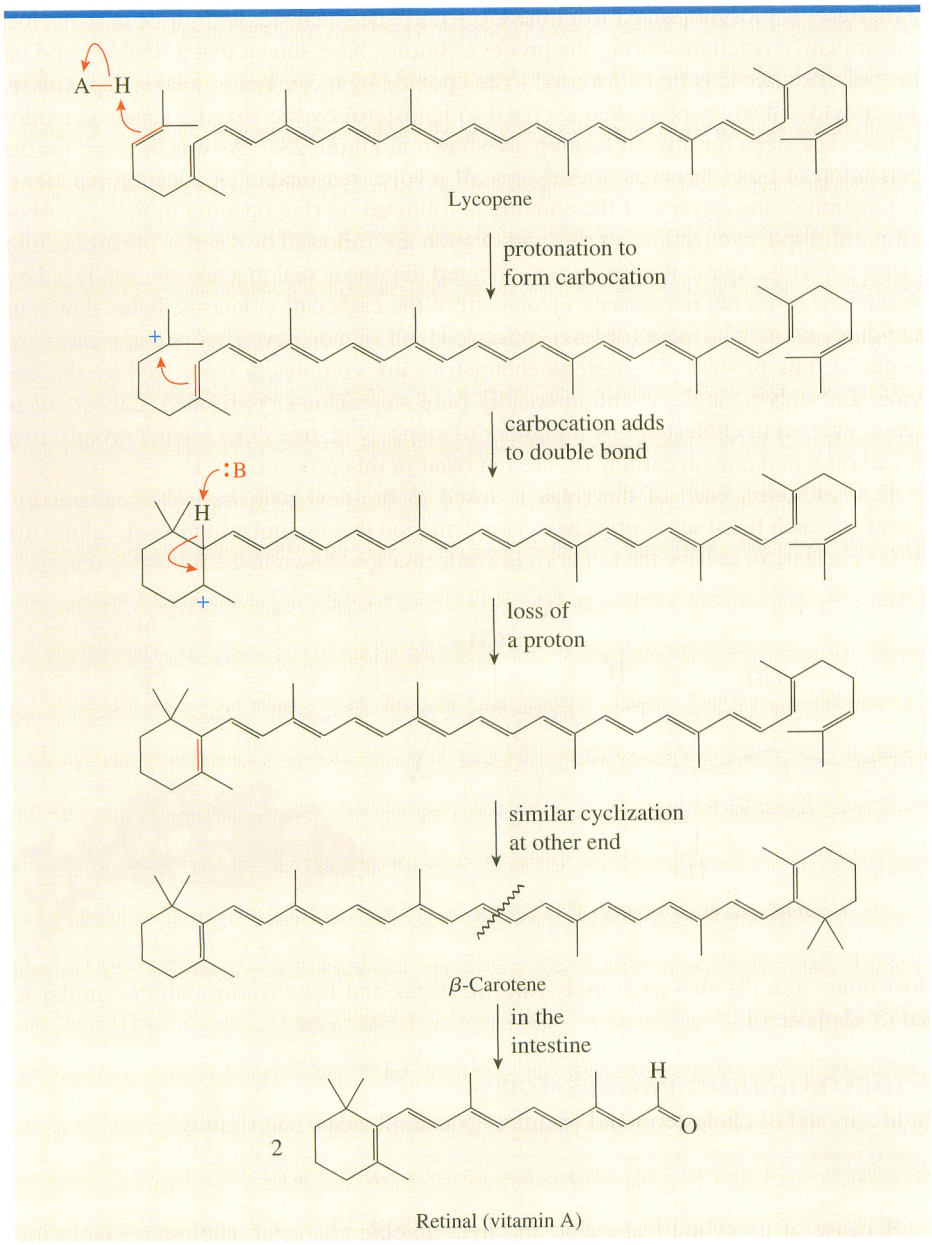
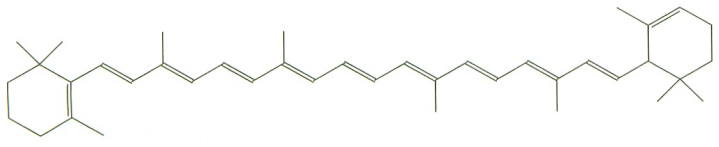


Figure 28.6

THE CONVERSION OF LYCOPENE TO β-CAROTENE AND VITAMIN A.

PROBLEM 28.15

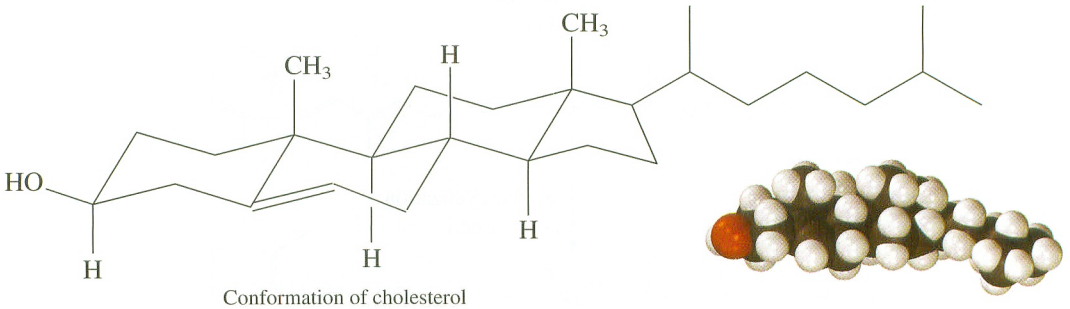
Small amounts of α-carotene are formed along with β-carotene in the process shown in Figure 28.6. Suggest a mechanism for this process and explain why more β-carotene is produced.



α-Carotene

Cholesterol is biosynthesized from the C_{30} triterpene squalene, with three carbons lost in degradative reactions during the process. Studies have shown that a double bond on one end of squalene is first converted to an epoxide by the enzyme squalene epoxidase. The epoxidized squalene is then cyclized to lanosterol by the enzyme squalene oxidocyclase. The steps for this cyclization are shown in Figure 28.7. As was the case for the cyclization of other terpenes, these steps all involve reasonable carbocation reactions. Protonation of the oxygen of the epoxide is followed by ring opening to form a carbocation. Multiple cyclizations of this carbocation are followed by a series of carbocation rearrangements. Again, it must be remembered that the actual mechanism, catalyzed by the enzyme, does not necessarily involve all of the carbocation intermediates shown in the figure and may be more (or less) concerted than shown. Seven new stereocenters are created in this process. Their stereochemistries are completely controlled by the enzyme, and only a single, enantiomerically pure stereoisomer is formed. Lanosterol is then converted to cholesterol by a number of steps. Note that three methyl groups, two on carbon 4 and one on carbon 14, are removed in this process.

In cholesterol, each of the rings is fused to the next with *trans*-stereochemistry. Therefore, each fused set of rings has a conformation that is similar to *trans*-decalin. This causes cholesterol to have the rather rigid conformation shown in the following diagram:



Conformation of cholesterol

Most other steroids also have *trans*-ring junctions and have conformations similar to that of cholesterol.

MODEL BUILDING PROBLEM 28.3

Build a model of cholesterol and examine its overall shape and rigidity.

Because of its cylindrical shape and hydrophobic character, cholesterol is an important component of the membranes of animal cells. Its rigid structure decreases membrane fluidity, but it also inhibits the "crystallization" of fatty acid side chains of the membrane lipids and it acts as a sort of membrane plasticizer.

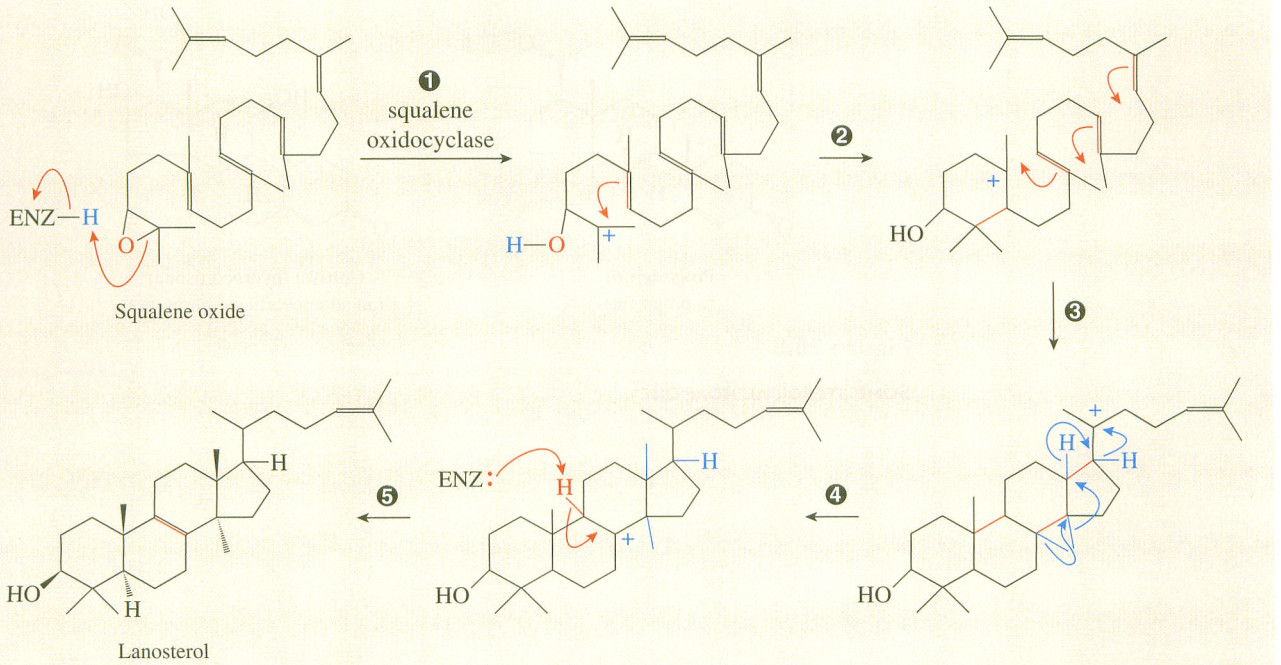
Other steroids, which are biosynthesized from cholesterol, show a wide variety of hormonal activity. The structures of a few of these steroidal hormones are shown in Figure 28.8. Testosterone is an androgen or male sex hormone, and estradiol is an estrogen or female sex hormone. Progesterone is a progestin and helps mediate the menstrual cycle and pregnancy. Cortisol (hydrocortisone) is a member of the class called adrenocortical hormones, which control metabolism, inflammation, and numerous other biological functions. It is interesting that the small differences in the structures of these compounds cause enormous differences in their physiological activities. For example, loss of the 19-methyl group of the male sex hormone testosterone and the aromatiza-

Squalene oxide is formed by epoxidation of squalene catalyzed by the enzyme squalene epoxidase.

❶ The cyclization is catalyzed by the enzyme squalene oxidocyclase. First the epoxide ring is protonated, and it then opens to form a carbocation.

❷ While the enzyme holds the molecule in a conformation favorable for cyclization, the carbocation adds to the double bond to form a six-membered ring and a new carbocation.

❸ This new carbocation adds to another double bond, and that carbocation adds to another. The enzyme controls both the stereochemistry and the regiochemistry of all of these additions, some of which may be concerted.



The product, lanosterol, is formed with complete regioselectivity and stereoselectivity.

❺ Finally a proton is removed by the enzyme to form a double bond.

❹ Next a series of carbocation rearrangements occurs. In each case, either a hydrogen or a methyl group moves to the adjacent carbon. These rearrangements may all be concerted.

Active Figure 28.7 ORGANIC Chemistry Now™

THE CYCLIZATION OF SQUALENE OXIDE TO LANOSTEROL. Test yourself on the concepts in this figure at **OrganicChemistryNow.**

tion of one cyclohexane ring produces the female sex hormone estradiol. In fact, estradiol is synthesized from testosterone in females.

PROBLEM 28.16

Explain the regiochemistry of the opening of the epoxide ring that occurs in the first step of the process shown in Figure 28.7.

PROBLEM 28.17

Assume that each cyclization or rearrangement shown in Figure 28.7 produces a discrete carbocation intermediate. Show the structure of each carbocation and comment on the regiochemistry of each step. Do any of the steps proceed with unexpected regiochemistry?

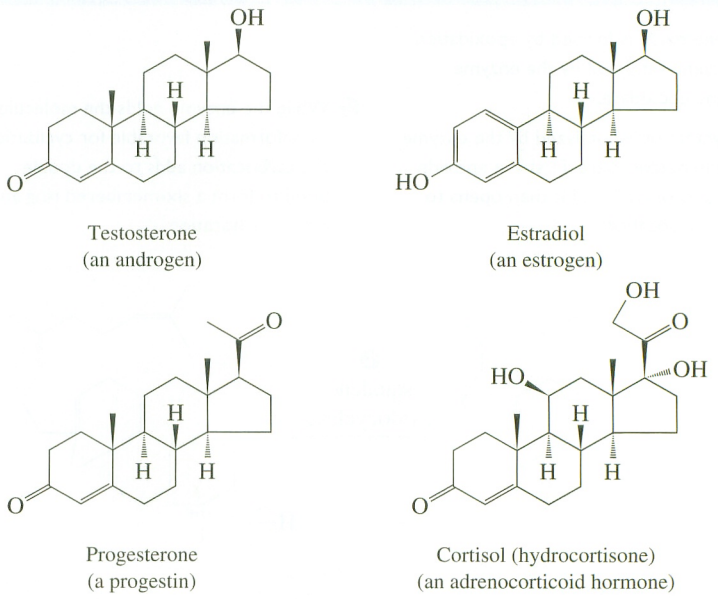


Figure 28.8

SOME STEROIDAL HORMONES.

Focus On

Syntheses That Mimic Nature

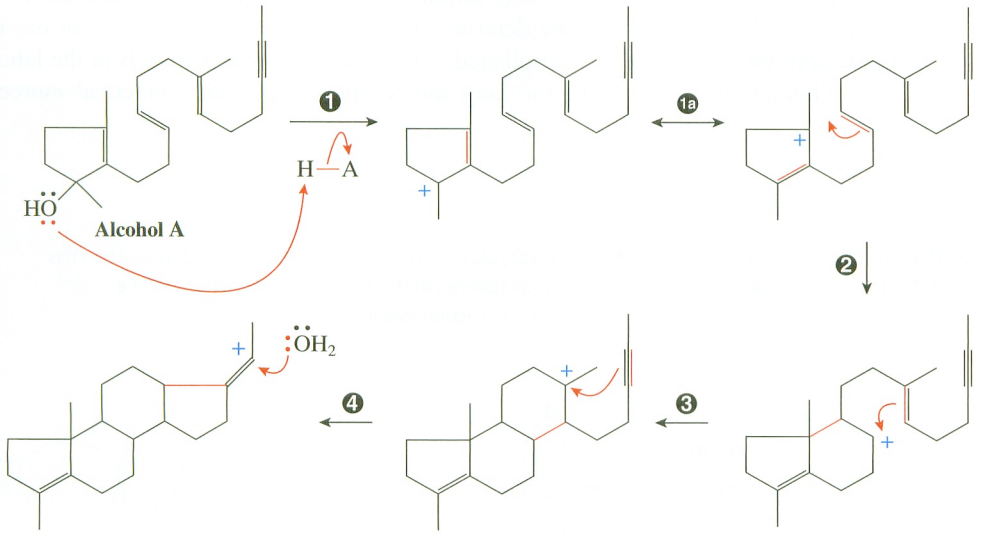
Nature often provides excellent suggestions about how to synthesize a compound. After the pathway for the biosynthesis of steroids by cationic cyclization of polyenes was determined, Professor William S. Johnson and coworkers at Stanford University used a very similar reaction to synthesize progesterone. The last part of this synthesis is outlined in the following equations. Alcohol **A** was prepared in 12 steps with an overall yield of 10%. It was then cyclized to form the steroid ring system.

This cyclization of **A** to form **B** is truly amazing. In a single step, three rings are formed, in 71% yield, predominantly with the correct stereochemistry. And this occurs without the aid of enzymes. Although the natural process proceeds in higher yield and is more stereoselective, we see again that the enzyme does not perform magic in the case of these cyclization reactions, but simply makes a reaction that is already favorable the only reaction that occurs.

❶ Protonation of the hydroxy group, followed by the loss of water, produces the carbocation that initiates the cyclization.

❶a This carbocation is allylic and is stabilized by resonance.

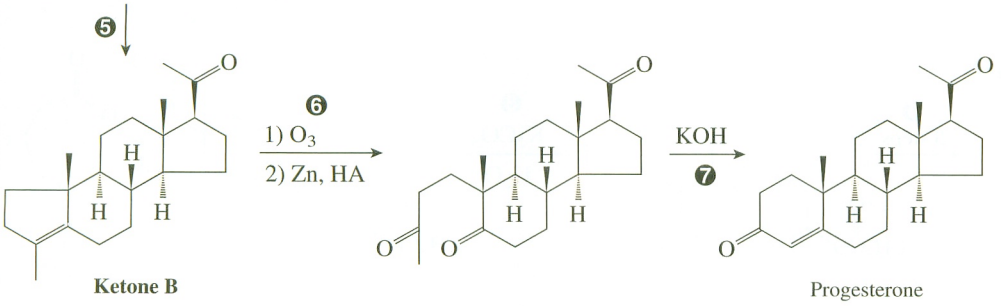
❷ The carbocation adds to the double bond to form a new six-membered ring.



❸ This new carbocation adds to the next double bond to form another six-membered ring.

❹ This carbocation adds to the triple bond, forming a five-membered ring and a vinyl cation.

❺ Water adds to this final cationic intermediate to form an enol, which then tautomerizes to the final product of the cyclization, ketone **B**.



Ketone B

Progesterone

Ketone **B** is formed in 71% yield from **A** in a single step. This step has formed three new rings. Although several stereoisomers are produced, the major product is **B**, which has the correct stereochemistry for conversion to racemic progesterone. To finish the synthesis, it is only necessary to open the five-membered ring and reclose it as a six-membered ring.

❻ Ozonolysis (Section 11.11) is used to open the ring.

❼ An intramolecular aldol condensation (Section 20.5) produces progesterone in 45% overall yield from **B**.

28.6 SYNTHESIS OF STEROIDS

Steroids are very powerful hormones and therefore are present in animals in only extremely minute concentrations. They are difficult to obtain from natural sources. For example, 4 tons of sow ovaries (from 80,000 pigs) were required to isolate the 12 mg of estrogen that was used for the determination of its structure. Syntheses of most of these hormones have been accomplished from simple starting materials in the laboratory. Although these routes are too long and complex to provide a practical source of

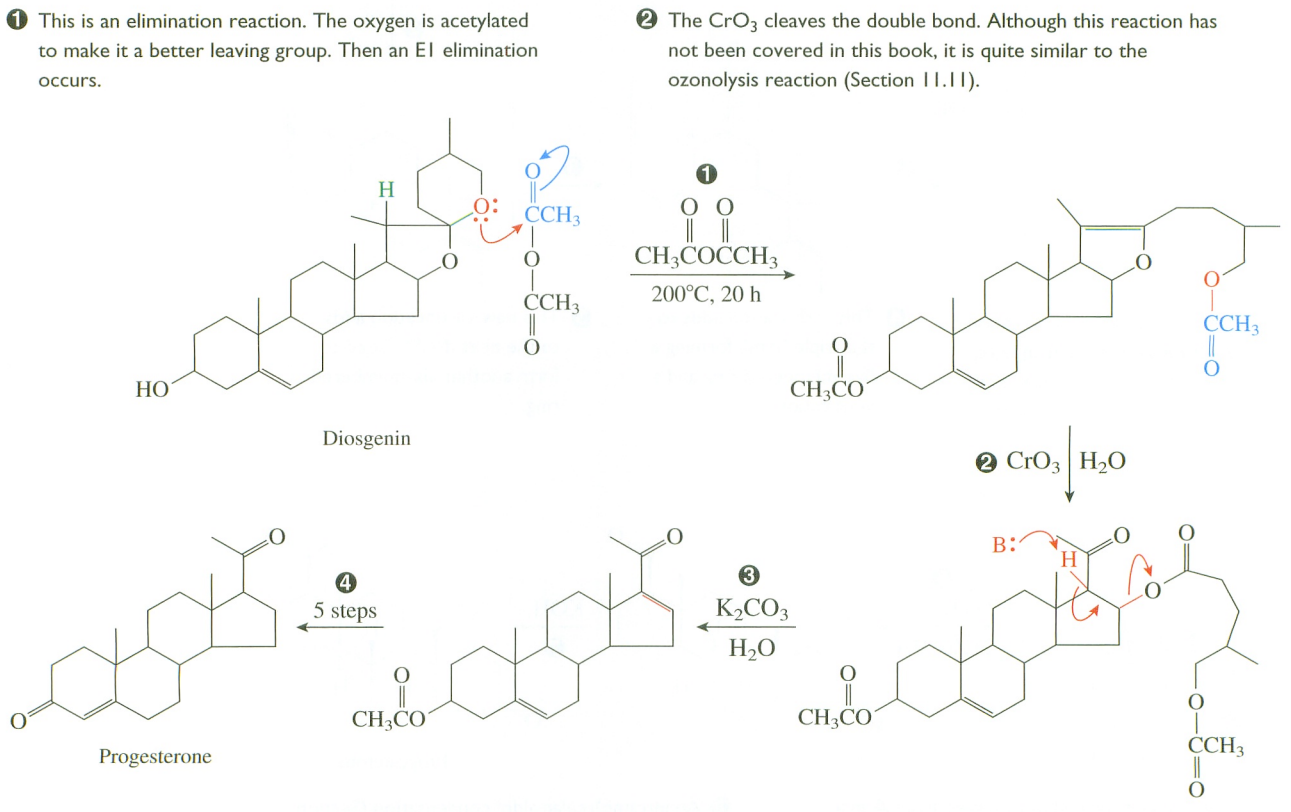

1 This is an elimination reaction. The oxygen is acetylated to make it a better leaving group. Then an E1 elimination occurs.
2 The CrO_3 cleaves the double bond. Although this reaction has not been covered in this book, it is quite similar to the ozonolysis reaction (Section 11.11).
Diosgenin
1
CH_3COCCH_3
200°C, 20 h
2 CrO_3 H_2O
B:
3
K_2CO_3
H_2O
4
5 steps
Progesterone
4 To complete the synthesis of progesterone, it is necessary to selectively reduce one of the double bonds, hydrolyze the acetate group to a hydroxy group, oxidize the hydroxy group to a carbonyl group, and isomerize the remaining double bond into conjugation with the carbonyl group. This is accomplished in five steps.
3 The ester group is lost by an elimination reaction. The adjacent carbonyl group makes the hydrogen more acidic, so it is more readily removed by the base. This is an example of an E1cb mechanism. (See the Focus On box on page 333.)

Figure 28.9

THE PREPARATION OF PROGESTERONE FROM DIOSGENIN.

the hormones for medicinal uses, many are truly elegant. R. B. Woodward, regarded by many as the greatest organic chemist of the last half of the twentieth century, was awarded the 1965 Nobel Prize in chemistry for his syntheses of steroids and numerous other natural products. (To aid in understanding the stereochemistry of some of the synthetic reactions he was using, he and R. Hoffmann developed the theory that explained the selectivity of pericyclic reactions [see Chapter 22]. Woodward died in 1979, or he would certainly have shared in the Nobel Prize awarded to Hoffmann and Fukui in 1981 and he would have been one of the few scientists to have won two Nobel Prizes.)

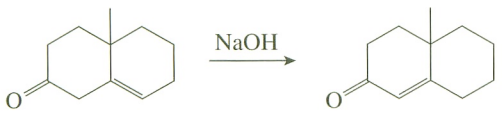
The most viable method for obtaining larger amounts of steroid hormones is to start with some readily available natural product with a structure that is similar to a steroid and convert it to the desired compound. Russell Marker, a professor at Pennsylvania State University, developed such a method to prepare progesterone from diosgenin, a material that is readily available from Mexican yams. His synthesis is outlined in Figure 28.9. However, he could not interest a major pharmaceutical company in his process, so in 1944 he founded his own company, Syntex, in Mexico City to develop it.

PROBLEM 28.18

Show a mechanism for the elimination reaction that occurs in the first step of the process shown in Figure 28.9.

PROBLEM 28.19

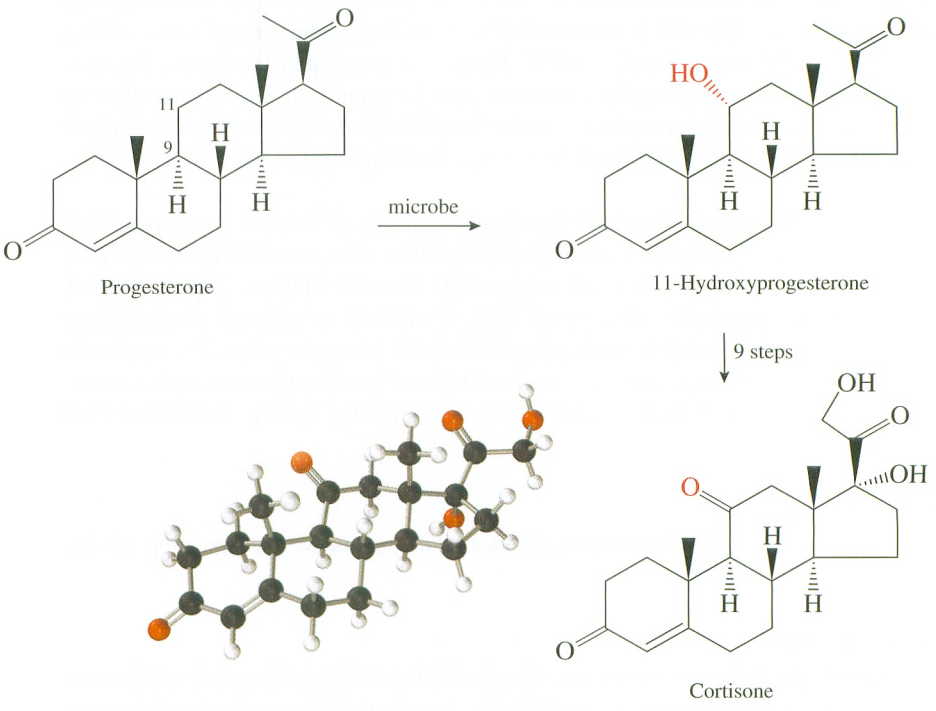
One way to accomplish the isomerization of a double bond into conjugation with a carbonyl group, one of the reactions needed for the last part of the synthesis of progesterone from diosgenin, is to treat the compound with base as shown in the following equation. Show a mechanism for this reaction.



In the late 1940s, cortisone was the most sought-after steroid because its anti-inflammatory properties appeared to have amazing effects in the treatment of rheumatoid arthritis. The major difficulty in converting a readily available steroid, such as progesterone, to cortisone was the introduction of an oxygen functionality at carbon 11. As we have seen innumerable times, reactions occur at a functional group or sometimes at the carbon adjacent to it. Causing a reaction to occur specifically at an unactivated carbon presents quite a challenge. The problem was solved by a roundabout method that introduced a double bond between carbons 9 and 11. Several syntheses of cortisone were reported in 1951.

However, some chemists at Upjohn found a better method. They were able to introduce the troublesome oxygen at carbon 11 by the microbiological fermentation of progesterone to produce 11-hydroxyprogesterone. The microbe, with its highly specific enzymes, was able to accomplish in a single step what required numerous steps for the

synthetic chemist. The completion of the synthesis of cortisone required only nine additional steps.

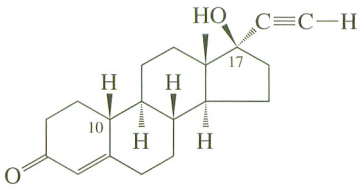


Focus On

The Birth Control Pill

Perhaps no single development has influenced today's society more than the birth control pill. This simple, effective, and inexpensive method to limit pregnancy helped bring about both the sexual revolution and women's liberation.

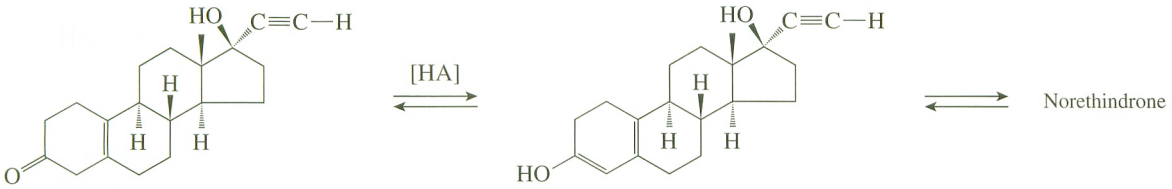
By 1937 it was known that large doses of progesterone inhibited ovulation, and the possibility of its use in birth control was recognized. A major problem, however, was that progesterone displays only weak activity when administered orally. The idea of an injectable contraceptive was not very attractive. Somewhat later, it was discovered that the removal of the methyl group from carbon 10 of progesterone makes it more active. Other researchers discovered that the incorporation of an ethynyl group at position 17 increased the oral activity of these drugs. Carl Djerassi at Syntex decided to combine both of these effects and prepared norethindrone. This compound was found to be an effective oral contraceptive and was quickly patented in 1951.



Norethindrone

Although norethindrone was the first oral contraceptive to be developed, it was not the first to be marketed. This was due mainly to the lack of both biological testing laboratories and marketing expertise at Syntex.

In 1953, G. D. Searle and Co. patented a related compound, norethynodrel. This steroid is also an active contraceptive when taken orally. This fact is not at all surprising to an experienced organic chemist because it is well known that a CC double bond such as the one in norethynodrel is readily isomerized into conjugation with a carbonyl group. This acid-catalyzed isomerization occurs via an enol intermediate, and the equilibrium favors the more stable, conjugated compound. The acidic conditions in the human gastric system are quite sufficient to accomplish the transformation of norethynodrel to norethindrone. It seems that chemical reactions do not care much about patents!



Norethynodrel

Syntex licensed norethindrone to Parke-Davis for development. Eventually, Parke-Davis decided not to market it because of fears about a possible boycott of their other products by groups who were opposed to birth control. Searle had no such concerns and brought its pill to the market in 1960 under the name Enovid. In the meantime, Syntex was forced to find another partner and finally settled on the Ortho division of Johnson & Johnson. The norethindrone pill was first marketed in 1962 under the name Ortho-Novum. By 1965 "the pill" was the most popular form of birth control.

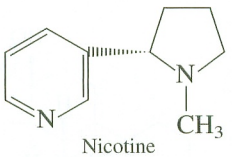
Progestin-based contraceptives work by inducing a state of pseudopregnancy. Therefore, they are administered in a 20-day cycle, followed by a break to allow normal menstruation. Today, most birth control pills use norethindrone or norgestrel, which is similar to norethindrone but has an ethyl group at position 13 rather than a methyl group. In addition, they contain a small amount of estrogen to reduce breakthrough bleeding. Interestingly, the usefulness of estrogen was discovered by accident when one batch of pills was synthesized with a small amount of estrogen as a contaminant.

There has been considerable concern about the health effects of the pill, and many studies have been done. These are extremely powerful compounds and are taken by a large number of healthy women over an extended period, not to cure disease, but to prevent pregnancy. Although there was some evidence for heightened risk of cardiovascular disease in early studies, this risk decreased as the amount of estrogen in the pill was decreased. Today, the amount of estrogen has been reduced from 150 μg per pill for *Enovid* to 30 to 35 μg per pill. The progestin component has also been reduced, and the pill is a relatively safe method of birth control.

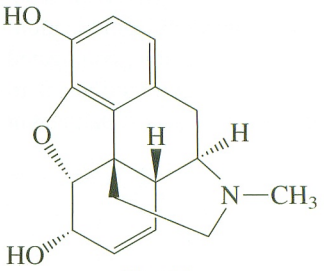
28.7 ALKALOIDS

Alkaloids are a group of nitrogen-containing natural products that occur primarily in higher plants, although they are also found in some fungi, such as mushrooms. The name alkaloid (meaning "alkali-like") is applied because they are amines and thus basic. Their basic character allows them to be readily isolated from their plant source. The plant material is extracted with aqueous acid. This converts the alkaloid to an ammonium cation, which is water soluble. Neutralization of the acidic extract with base causes the alkaloid to precipitate.

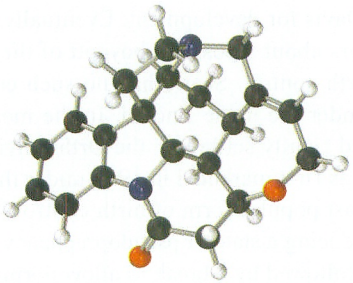
Like terpenes, alkaloids have been important in the development of organic chemistry. Some, such as nicotine, have relatively simple structures. Others, such as morphine and strychnine, have very complex structures containing multiple rings. Most are quite physiologically active.

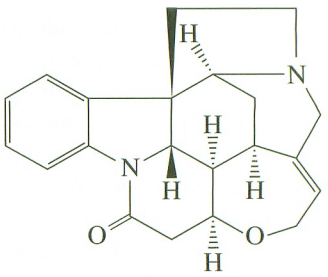


Nicotine
(the addictive substance in tobacco)



Morphine
(a highly addictive painkiller obtained from the opium poppy)





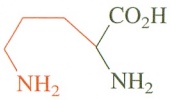
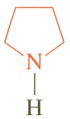
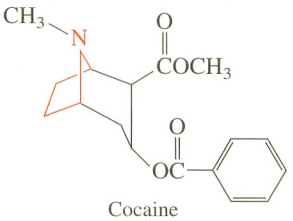
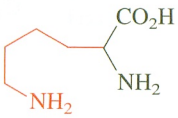
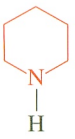
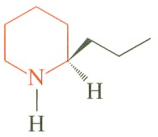
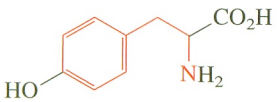
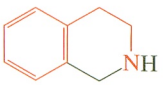
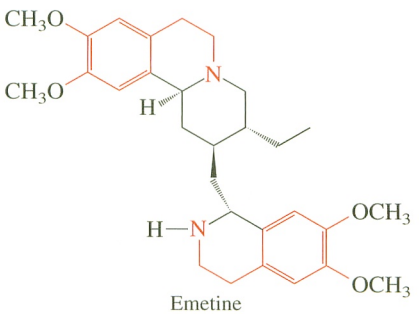
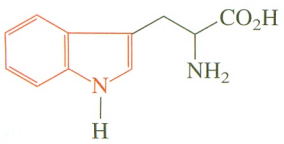
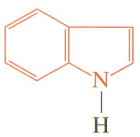
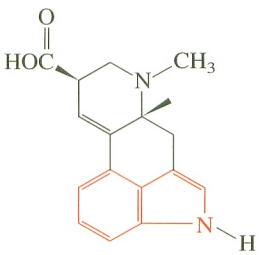
Strychnine
(an extremely poisonous central nervous system stimulant)

The complex structures of alkaloids, along with their biological activity and relative ease of isolation, have kept the interest of organic chemists over the years. They have provided enormously challenging structure elucidation problems. For example, although strychnine was first isolated in 1818, its complete structure was not determined until 1946. (R. Robinson was awarded the 1947 Nobel Prize in chemistry for the determination of the structure of strychnine and other alkaloids as well as synthetic work in this area.) Of course, soon after this, synthetic chemists accepted the challenge of preparing this complicated compound in the laboratory. The first synthesis, reported by

Woodward in 1953, required 28 steps (not very many when the complexity of the molecule is considered). More recently, strychnine has been prepared, enantiomerically pure, in 20 steps with an overall yield of 3%!

Just as terpenes could be viewed as being formed from isoprene units, alkaloids can be viewed as being derived from amino acids. Four amino acids give rise to important classes of alkaloids. As shown in Table 28.1, the pyrrolidine alkaloids are derived from the amino acid ornithine (not one of the 20 "standard" amino acids), the piperidine alkaloids from lysine, the isoquinoline alkaloids from tyrosine, and the indole alkaloids from tryptophan.

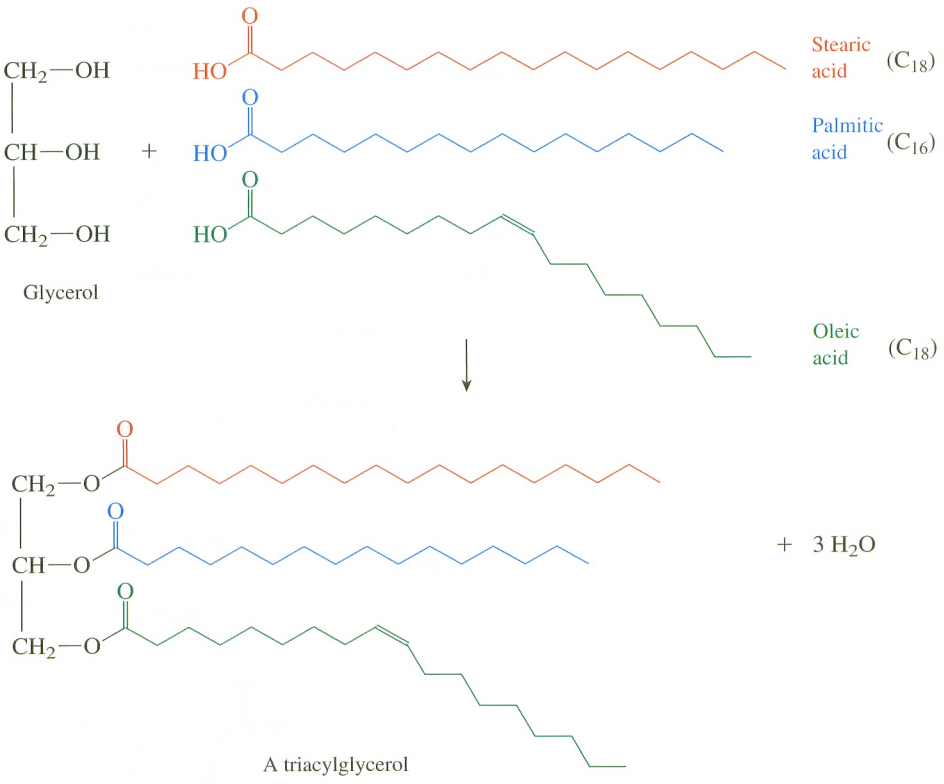
Table 28.1 Some Important Classes of Alkaloids

Amino Acid	Alkaloid Partial Structure	Example	
 Ornithine	 Pyrrolidine	 Cocaine	Cocaine is a central nervous system stimulant; it is obtained from the coca plant.
 Lysine	 Piperidine	 Coniine	Coniine is a major component of poisonous hemlock, which was used to kill Socrates.
 Tyrosine	 Isoquinoline	 Emetine	Emetine is used to treat amebic dysentery.
 Tryptophan	 Indole	 Lysergic acid	Lysergic acid is an ergot alkaloid that is obtained from a fungus that grows on cereal. The diethyl amide is the hallucinogen LSD.

As was the case with terpenes, the function of alkaloids in plants is not known. It has been proposed that they are merely nitrogen-containing waste products of plants, like urea in animals. However, most plants reutilize nitrogen, rather than wasting it. Furthermore, it is difficult to imagine why such complex structures would be needed to store waste nitrogen. Like terpenes, alkaloids have been proposed to serve as protection from herbivores and insects. However, only a few examples of such protection can be demonstrated. Whatever the role of alkaloids is, some 70% to 80% of plants manage to do quite nicely without them.

28.8 Fats and Related Compounds

As discussed briefly in the Focus On box titled "The Preparation of Soap" in Chapter 19, fats are triesters formed from glycerol and long, linear-chain carboxylic acids, known as fatty acids. The resulting triesters are called **triacylglycerols.** Stearic, palmitic, and oleic acids are among the many different fatty acids that occur in nature:



A triacylglycerol

Fatty acids usually have an even number of carbons because they are biosynthesized from acetate ion, which has two carbons. Those with 14, 16, 18, and 20 carbons are most common. Their biosynthesis is outlined in Figure 28.10. They may be saturated, like stearic acid and palmitic acid, or they may have one or more CC double bonds, like

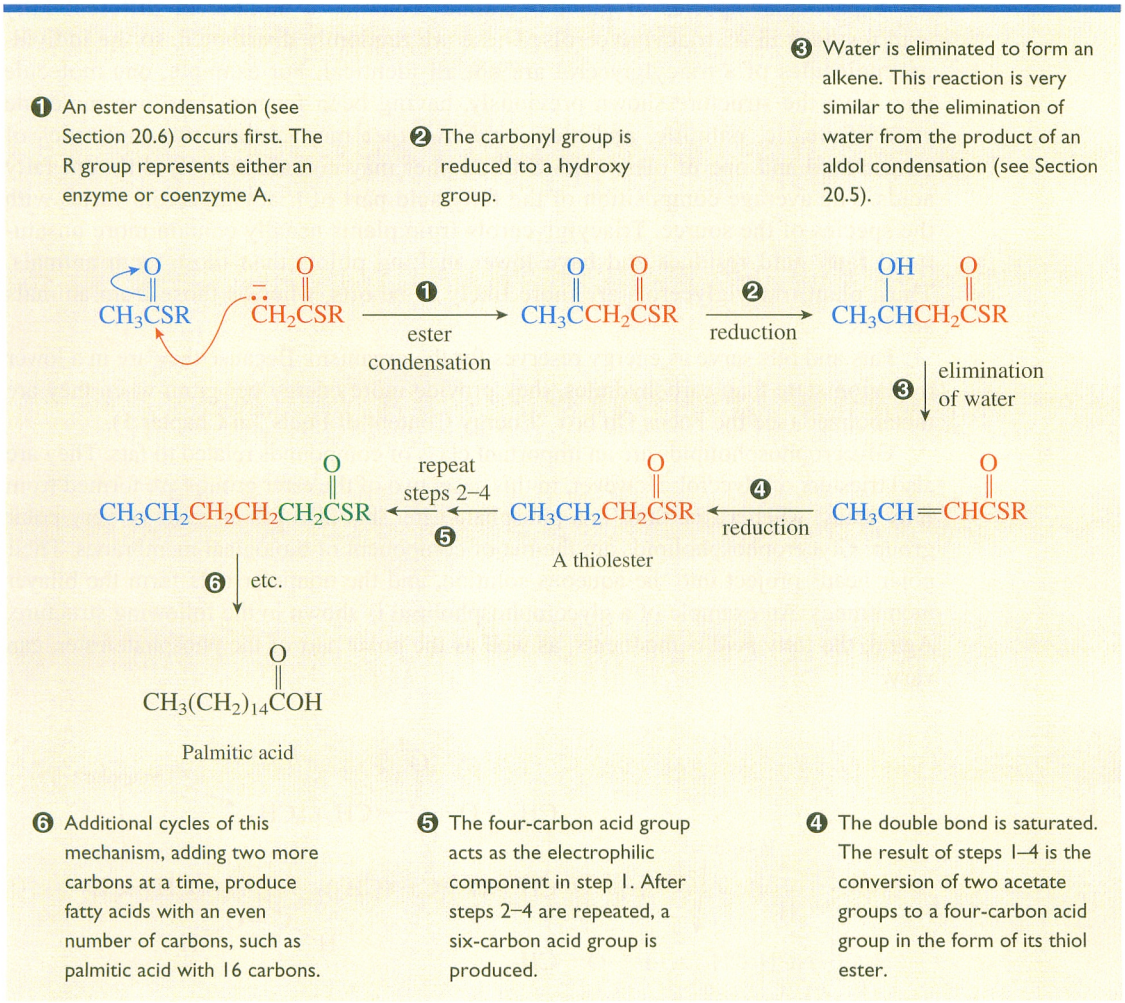

❶ An ester condensation (see Section 20.6) occurs first. The R group represents either an enzyme or coenzyme A.
❷ The carbonyl group is reduced to a hydroxy group.
❸ Water is eliminated to form an alkene. This reaction is very similar to the elimination of water from the product of an aldol condensation (see Section 20.5).
CH3CSR
CH2CSR
ester condensation
CH3CCH2CSR
reduction
CH3CHCH2CSR
elimination of water
CH3CH2CH2CH2CH2CSR
repeat steps 2–4
CH3CH2CH2CSR
A thiolester
reduction
CH3CH=CHCSR
etc.
CH3(CH2)14COH
Palmitic acid
❻ Additional cycles of this mechanism, adding two more carbons at a time, produce fatty acids with an even number of carbons, such as palmitic acid with 16 carbons.
❺ The four-carbon acid group acts as the electrophilic component in step 1. After steps 2–4 are repeated, a six-carbon acid group is produced.
❹ The double bond is saturated. The result of steps 1–4 is the conversion of two acetate groups to a four-carbon acid group in the form of its thiol ester.

Figure 28.10

THE BIOSYNTHESIS OF FATTY ACIDS.

oleic acid. The double bonds invariably have cis geometry, and the kink in the long chain caused by the cis double bond prevents the chain from packing as well into a crystal lattice and decreases the melting point of the lipid. Thus, oils tend to have a larger percentage of unsaturated fatty acids than fats.

PROBLEM 28.20

Show a mechanism for step 1 of Figure 28.10. Ignore the participation of the enzyme.

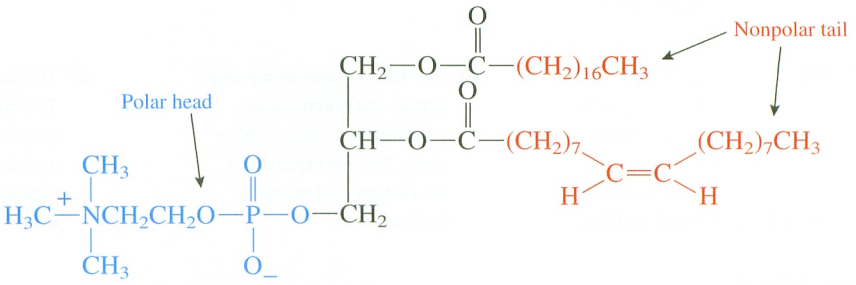
PROBLEM 28.21

Show a mechanism for step 3 of Figure 28.10. Assume that the reaction is catalyzed by base.

A particular species of plant or animal contains a number of different fatty acid residues in its triacylglycerols. These are randomly distributed, so the individual molecules of a triacylglycerol are not all identical. For example, one molecule may have the structure shown previously, having been formed from one molecule each of stearic, palmitic, and oleic acid. Another may contain two molecules of stearic acid and one of oleic acid. Still another may contain entirely different fatty acids. The average composition of the fatty acid part of triacylglycerols varies with the species of the source. Triacylglycerols from plants usually contain more unsaturated fatty acid residues and have lower melting points than those from animals. Thus, plant triacylglycerols are more likely to be oils, whereas those from animals are fats.

Fats and oils serve as energy reserves for the organism. Because they are in a lower oxidation state than carbohydrates, they provide more energy per gram when they are metabolized (see the Focus On box "Energy Content of Fuels" in Chapter 5).

Glycerophospholipids are an important class of compounds related to fats. They are also triesters of glycerol. However, in this case, two of the ester groups are formed from fatty acids, whereas the third is a phosphate ester that also has an ionic or very polar group. Glycerophospholipids are the major component of biological membranes. Their polar heads project into the aqueous solution, and the nonpolar tails form the bilayer membranes. An example of a glycerophospholipid is shown in the following structure. Again, the fatty acid components, as well as the polar part of the phosphate ester, can vary.

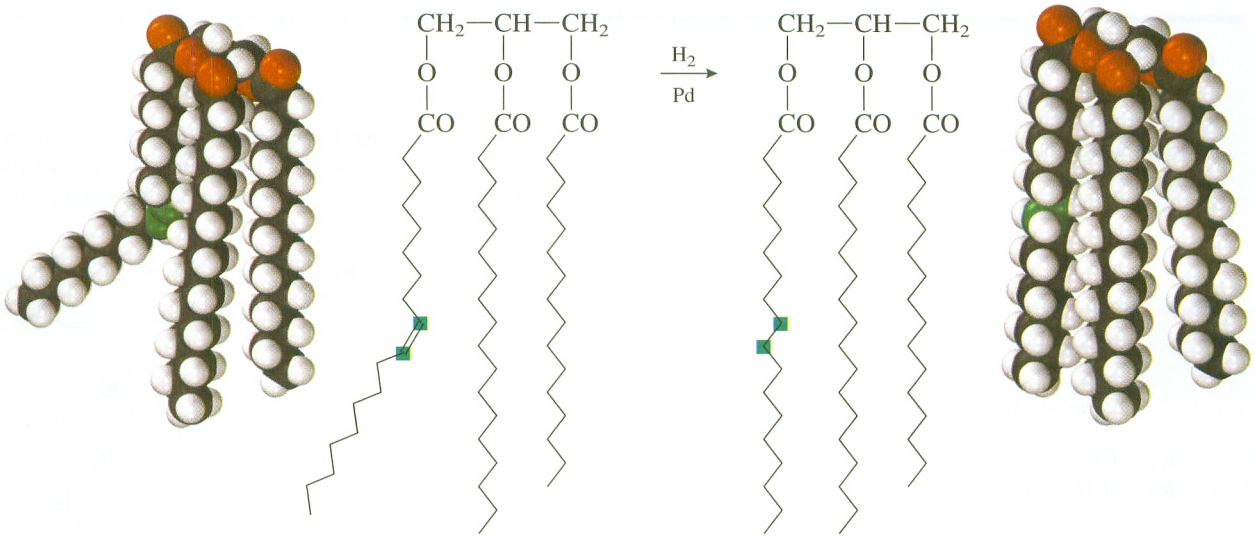


A glycerophospholipid

Focus On

Partially Hydrogenated Vegetable Oil

Margarines are prepared from vegetable oils. However, most people do not like to spread liquid oil on their toast. The presence of cis double bonds in the triacylglycerols causes kinks in the hydrocarbon tails of the fatty acid residues. These kinks prevent the triacylglycerol molecules from packing closely and lower the melting point. To raise the melting point of the oil so that it is a solid at room temperature, some of the double bonds are reduced by catalytic hydrogenation:

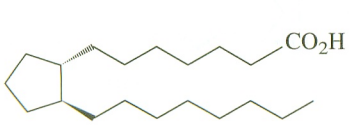


As more of the double bonds are saturated, the melting point of the product increases. The degree of hydrogenation is carefully controlled to produce a product with just the right melting point, a partially hydrogenated vegetable oil.

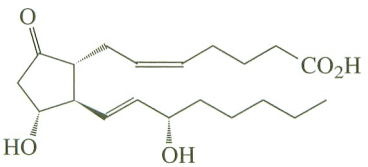
A product with a higher melting point is necessary for consumer acceptance. In addition, triacylglycerides that are more unsaturated tend to spoil more rapidly. This spoilage is due to oxidation caused by radical reactions. (This is an example of the autoxidation process described in Section 21.8 and the Focus On box "Vitamin E and Lipid Autoxidation" on page 937. The hydrogens on the allylic carbons of unsaturated fatty acid residues are more readily abstracted because the resulting radicals are stabilized by resonance, so these compounds oxidize and spoil faster.) However, there is a trade-off, because it has been demonstrated that saturated fats have more deleterious health consequences than unsaturated fats do.

28.9 PROSTAGLANDINS

Prostaglandins are naturally occurring carboxylic acids that are related to the fatty acids. They contain the carbon skeleton of prostanoic acid, with various additional unsaturations and oxygen groups. One example is provided by PGE_2:



Prostanoic acid



PGE_2

Prostaglandins have been found to be involved in a number of important physiological functions, including the inflammatory response, the production of pain and fever, the regulation of blood pressure, the induction of blood clotting, and the induction of labor.

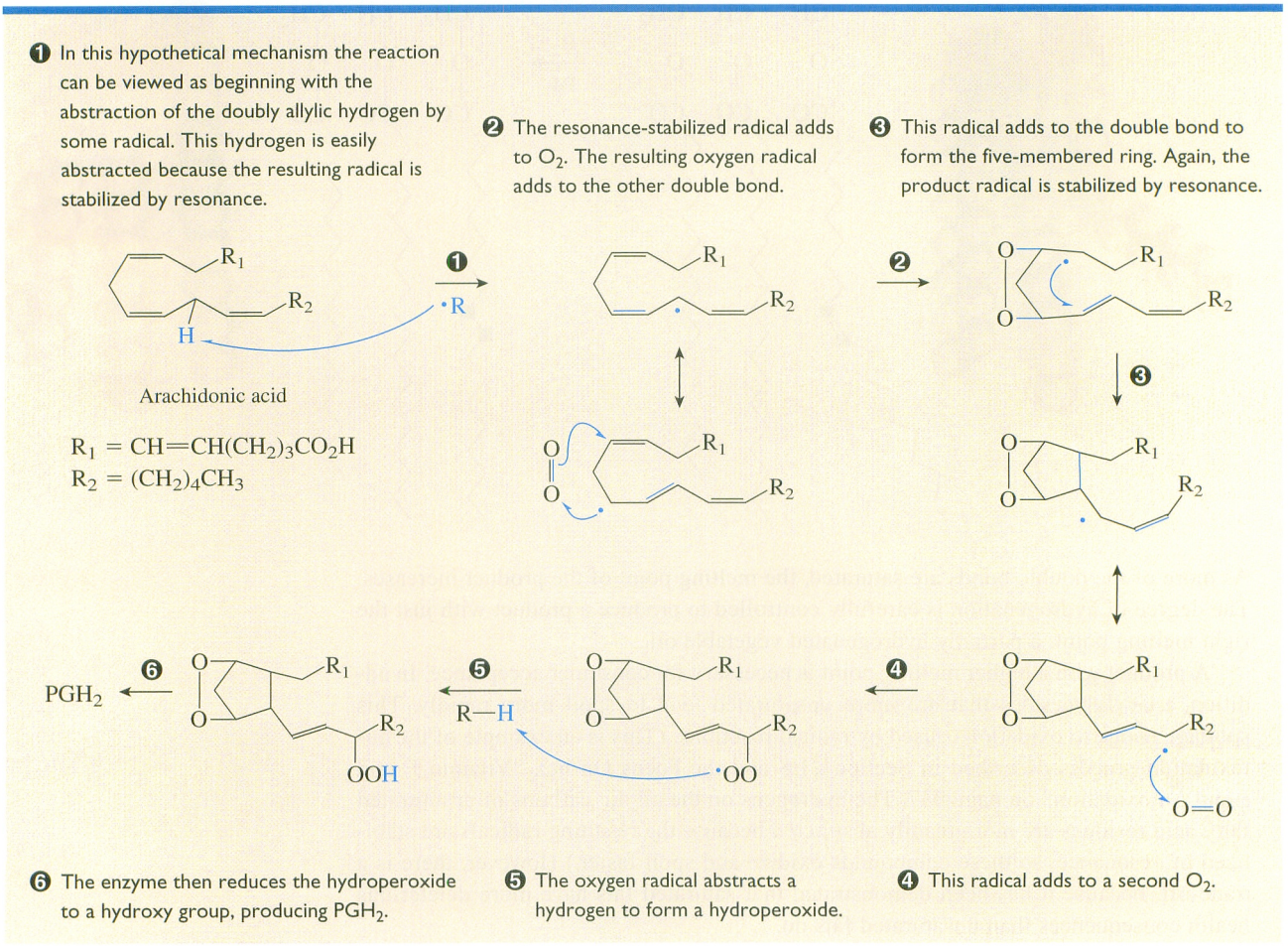
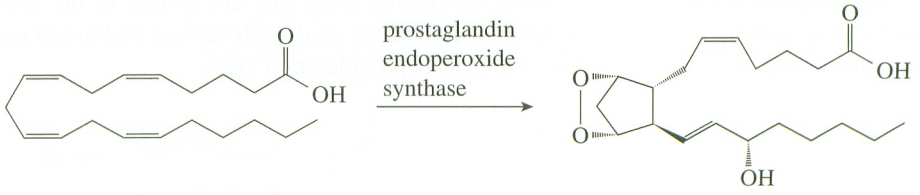

1 In this hypothetical mechanism the reaction can be viewed as beginning with the abstraction of the doubly allylic hydrogen by some radical. This hydrogen is easily abstracted because the resulting radical is stabilized by resonance.
2 The resonance-stabilized radical adds to O_2. The resulting oxygen radical adds to the other double bond.
3 This radical adds to the double bond to form the five-membered ring. Again, the product radical is stabilized by resonance.
Arachidonic acid
$R_1 = CH{=}CH(CH_2)_3CO_2H$
$R_2 = (CH_2)_4CH_3$
6 The enzyme then reduces the hydroperoxide to a hydroxy group, producing PGH_2.
5 The oxygen radical abstracts a hydrogen to form a hydroperoxide.
4 This radical adds to a second O_2.

Figure 28.11

HYPOTHETICAL "MECHANISM" OF THE FORMATION OF PGH_2 FROM ARACHIDONIC ACID.

Prostaglandins are biosynthesized from arachidonic acid, an unsaturated fatty acid containing four double bonds. The enzyme prostaglandin endoperoxide synthase converts arachidonic acid to PGH_2, which serves as the precursor for prostaglandins and related compounds. Aspirin exerts its pharmacological effect by inhibiting this enzyme.



Arachidonic acid PGH_2

Although the enzyme exerts enormous stereochemical and regiochemical control, the reaction that it catalyzes, like others in this chapter, involves only unexceptional chemical steps. A hypothetical "mechanism" for this process, based on radical chemistry, shows that the steps are, indeed, reasonable (see Figure 28.11). Again, remember that this does not represent the real mechanism, which is certainly more concerted than shown in the figure and probably does not involve any true radical intermediates.

Review of Mastery Goals

After completing this chapter, you should be able to:

- Recognize the general structural features associated with terpenes and how they can be viewed as being formed from isoprene units. (Problem 28.22)
- Understand the hypothetical mechanisms by which terpenes are formed. (Problems 28.25, 28.26, 28.27, 28.32, 28.33, and 28.35)
- Do the same for steroids and prostaglandins. (Problems 28.22, 28.28, 28.29, and 28.31)
- Recognize the general structural features of alkaloids and fats. (Problem 28.22)

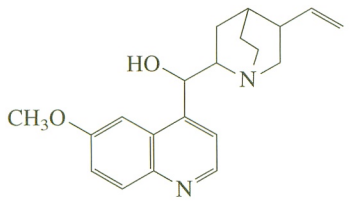
ORGANIC Chemistry Now™
Click *Mastery Goal Quiz* to test how well you have met these goals.

Additional Problems

ORGANIC Chemistry Now™
Assess your understanding of this chapter's topics with additional quizzing and conceptual-based problems at **http://now.brookscole.com/hornback2**

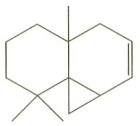
28.22 Identify each of these compounds as a terpene, steroid, alkaloid, fat, or prostaglandin:

a)



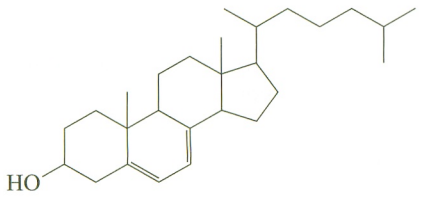
Quinine

b)



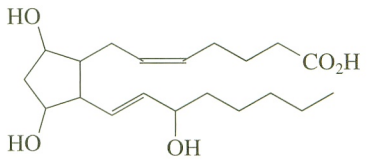
Thujopsene

c)

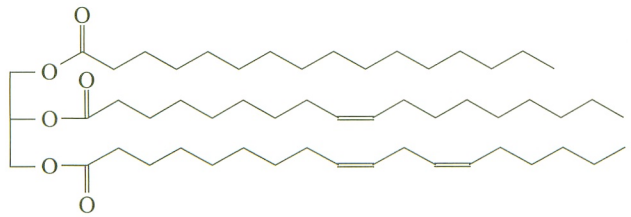


Provitamin D

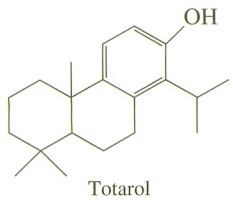
d)



e)



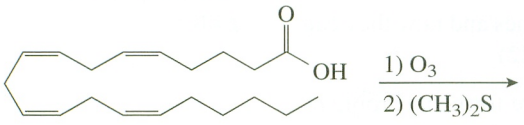
f)



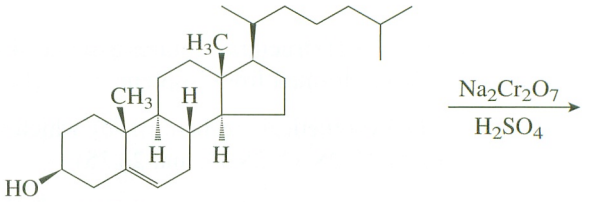
Totarol

28.23 Show the products of these reactions:

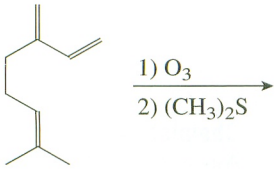
a)



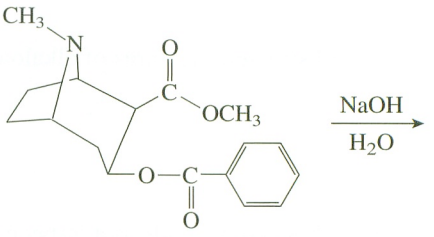
b)



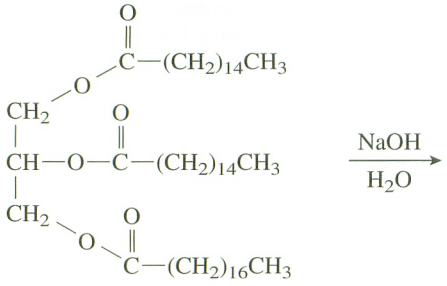
c)



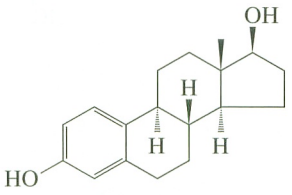
d)



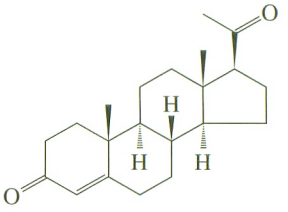
e)



28.24 Describe a method to easily separate estradiol from progesterone by taking advantage of their different chemical properties.



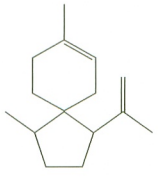
Estradiol



Progesterone

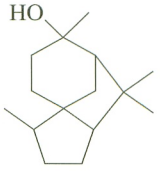
28.25 Show a mechanism for the formation of these compounds from farnesyl pyrophosphate:

a)



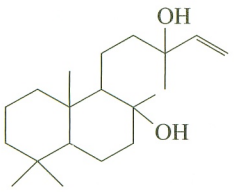
α-Acoradiene

b)



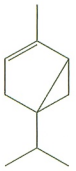
Cedrol

28.26 Show a mechanism for the formation of sclareol from geranylgeranyl pyrophosphate.



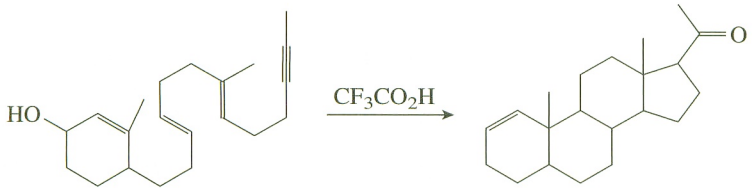
Sclareol

28.27 Show a mechanism for the formation of thujene from neryl pyrophosphate.



Thujene

28.28 Show a mechanism for this cyclization reaction:

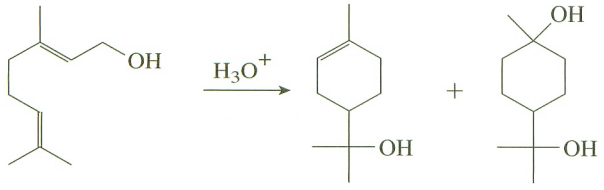


28.29 Show a mechanism for the final step in the synthesis of progesterone shown in the Focus On box "Syntheses That Mimic Nature."

28.30 Discuss the regiochemistry of each step in the conversion of alcohol **A** to ketone **B** in the Focus On box "Syntheses That Mimic Nature."

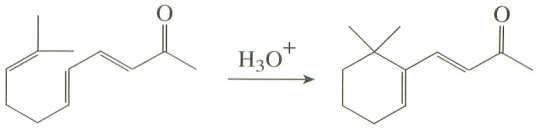
28.31 Show the steps in the mechanism for the conversion of norethynodrel to norethindrone discussed in the Focus On box "The Birth Control Pill."

28.32 Show a mechanism for the acid-catalyzed conversion of geraniol to α-terpineol and terpin:



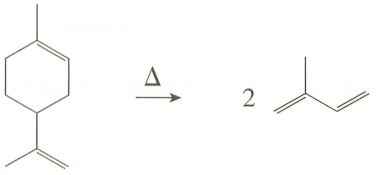
Geraniol α-Terpineol Terpin

28.33 Suggest a mechanism for the acid-catalyzed conversion of ψ-ionone to β-ionone:

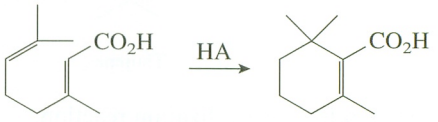


ψ-Ionone β-Ionone

28.34 Suggest a mechanism for the conversion of limonene to isoprene:



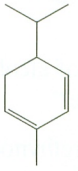
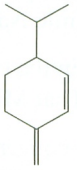
28.35 Suggest a mechanism for the cyclization of **A** and explain why **B** and **C** are unreactive under these conditions.



A

B **C**

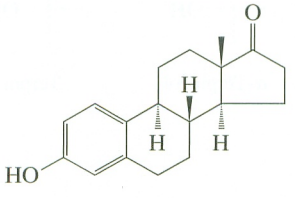
28.36 Show the products of ozonolysis of these terpenes:

a)  **b)** 

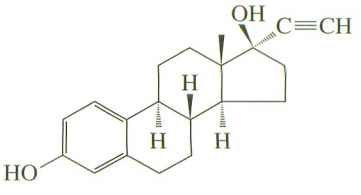
28.37 On ozonolysis, linolenic acid ($C_{18}H_{30}O_2$) gives the products shown in the following equation. Show the structure of linolenic acid.

Linolenic acid $\xrightarrow[2)\ (CH_3)_2S]{1)\ O_3}$

28.38 Suggest a synthesis of the synthetic estrogen ethynylestradiol from estrone.



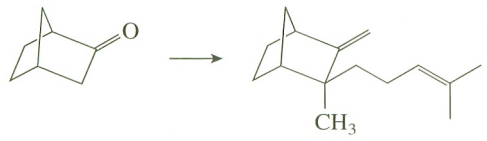
Estrone



Ethynylestradiol

28.39 Suggest syntheses of oleic acid and stearic acid starting from 1-decyne and 1-bromo-7-chloroheptane.

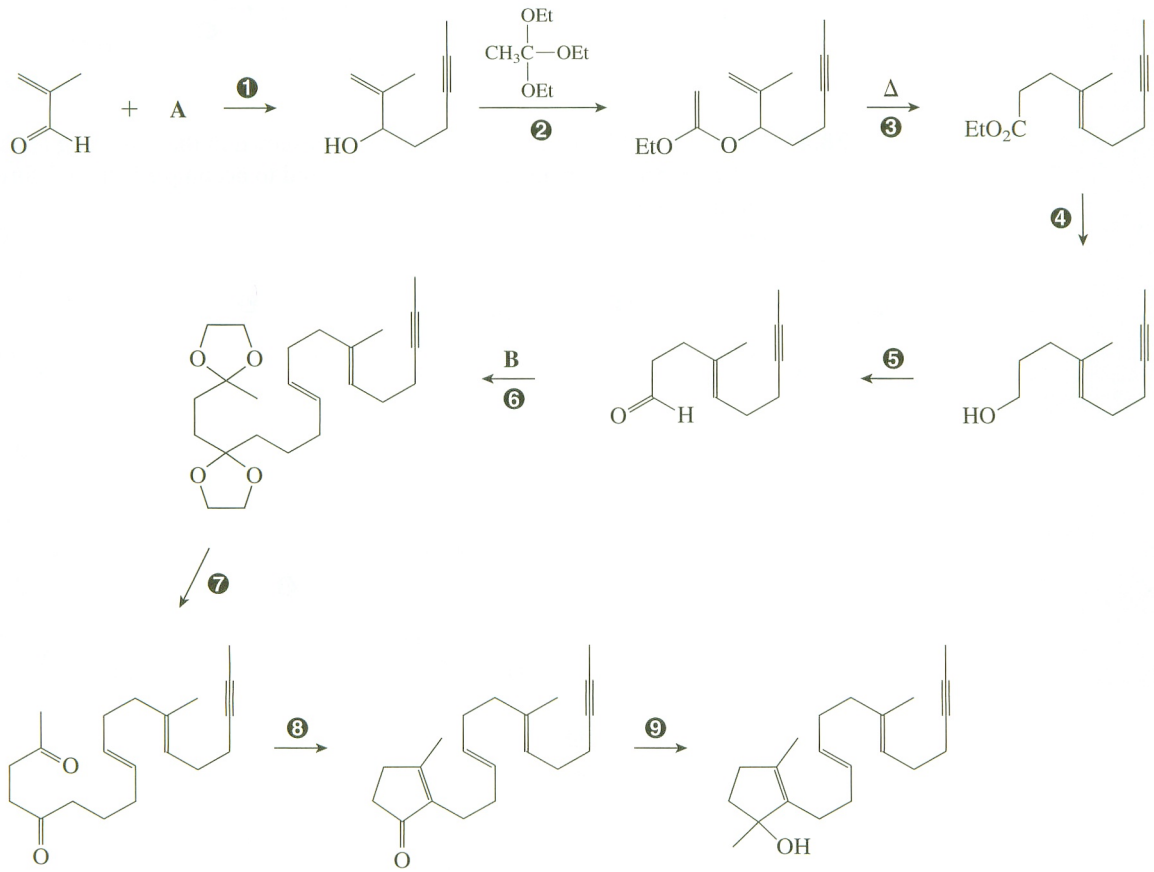
28.40 Suggest a synthesis of β-santalene from the following ketone. (Do not worry about stereochemistry.)



β-Santalene

28.41 The following reaction sequence was used to prepare the starting material for Johnson's synthesis of progesterone described in the Focus On box "Syntheses That Mimic Nature."

a) Show the reagents that are needed to accomplish steps 4, 5, 7, 8, and 9.
b) Show the structures of **A** and **B.**
c) Show the mechanism for step 3.
d) Show the mechanism for step 8.



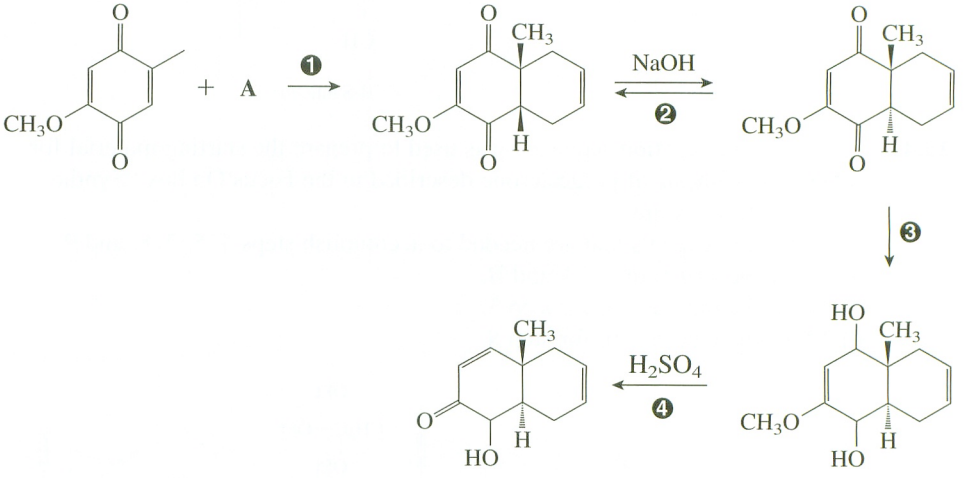
28.42 Part of Woodward's synthesis of cholesterol is shown in the following reaction scheme.

a) Show the structure of **A.** What kind of reaction is this?

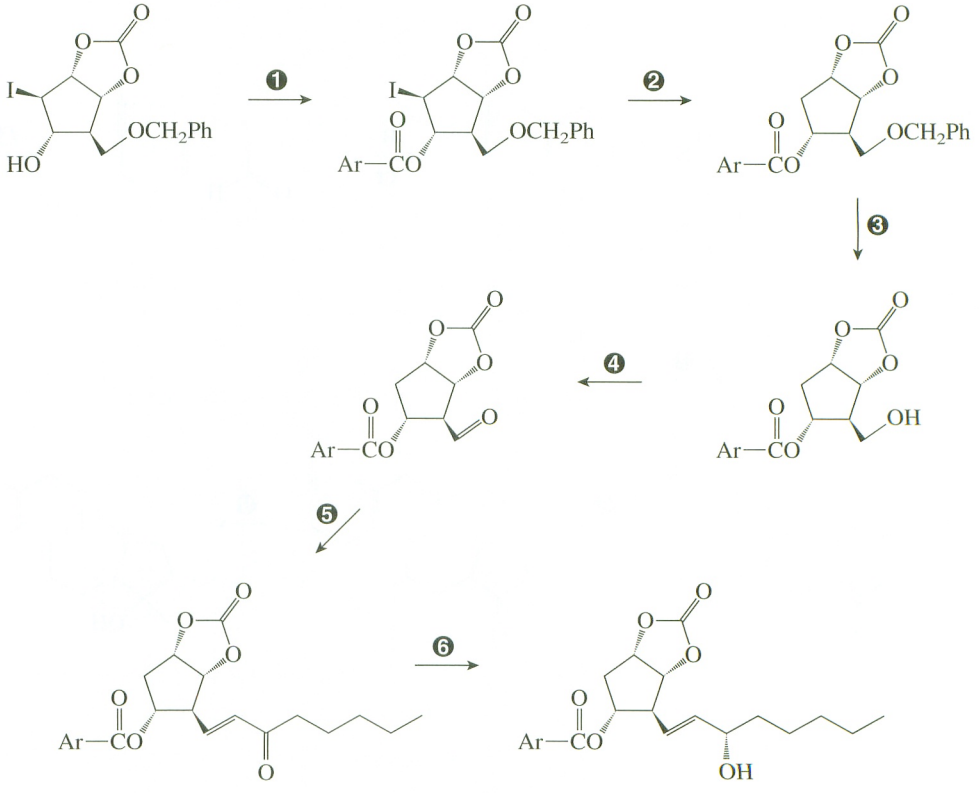
b) Show a mechanism for step 2. Explain which of these products you expect to dominate at equilibrium.

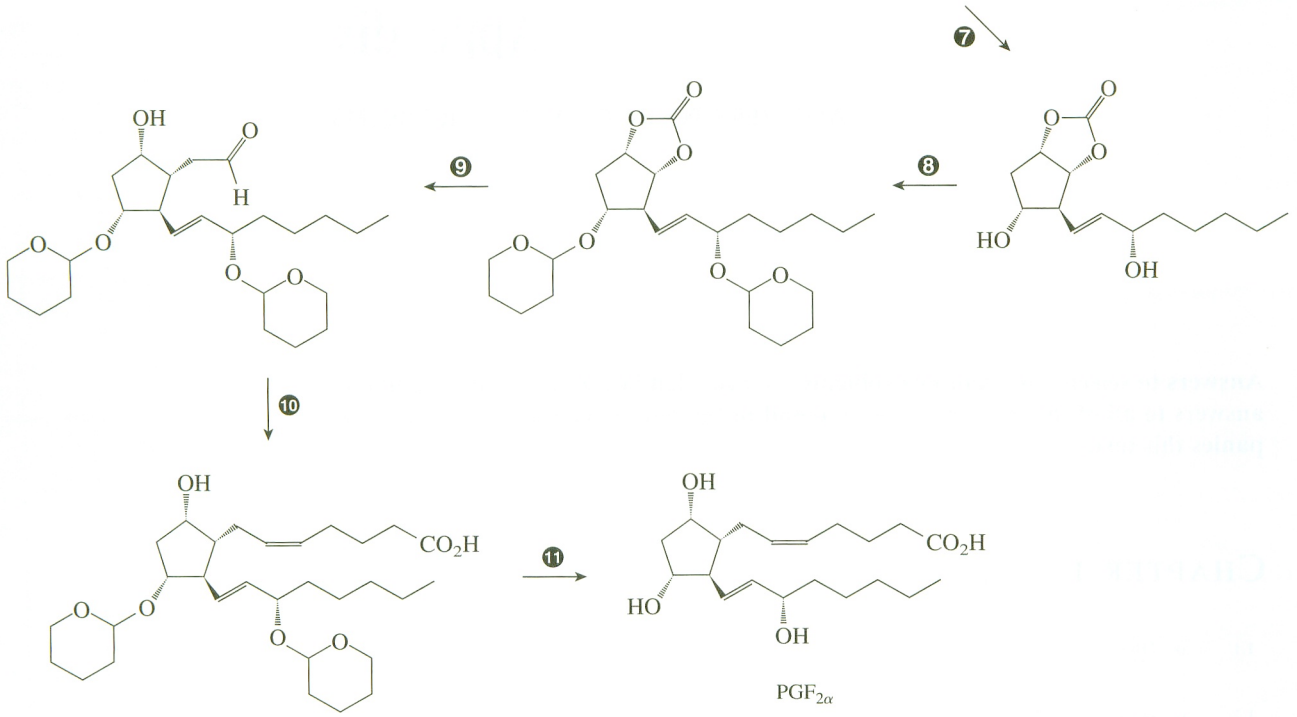
c) Suggest a reagent to accomplish step 3.

d) Show a mechanism for step 4.



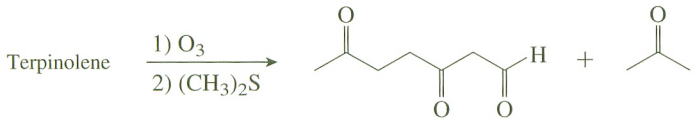
28.43 One of Corey's prostaglandin syntheses is shown in the following reaction scheme. Suggest reagents that could be used to accomplish steps 1 through 11 in this synthesis.





Problems Involving Spectroscopy

28.44 The terpene terpinolene, $C_{10}H_{16}$, gives compound **A**, $C_{10}H_{20}$, on reaction with H_2/Pt. **A** shows seven peaks in its ^{13}C-NMR spectrum. The products of ozonolysis of terpinolene are shown in the following equation. Show the structure of terpinolene.



Do you need a live tutor for homework problems? Access vMentor at Organic ChemistryNow at **http://now.brookscole.com/hornback2** for one-on-one tutoring from a chemistry expert.